

Abstracts and Research Assumptions Used in the Robertson Brain Chemistry Optimization and Performance Enhancement Programs

There are several hundred references to support concepts and theories applied in the Brain Chemistry Optimization and Performance Enhancement Programs. Understanding the relevance of selected research requires an understanding of how the conclusions of one study relate to other research outcomes. For example, some research will show the effect of exercise on cortisol. The next research shows the effect of cortisol on sympathomimetics. The next step would be to deduce that exercise affects sympathomimetics through alteration of cortisol in the same way the research indicated.

Our experts review brain chemistry research from around the world on a perpetual basis; evaluating which studies are legitimate science and applying that research to our symptom assessment tools. Following are some of the important abstracts used to formulate the initial broad based concepts and to monitor and update current recommendations.

[Activity Abstracts](#)

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Activity Abstracts:

Brain Res. 2004 Sep 3;1019(1-2):134-43. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Dopaminergic and serotonergic autoreceptor stimulation effects are equivalent and additive in the suppression of spontaneous and cocaine induced locomotor activity.** Carey RJ, DePalma G, Damianopoulos E, Hopkins A, Shanahan A, Muller CP, Huston JP. VA Medical Center, Syracuse, NY 13210, USA. PMID: 15306247 [PubMed - in process]

We used the D(2) receptor agonist, apomorphine (APO) and the 5-HT(1A) receptor agonist, 8OHDPAT (8OH) in a low dose range to stimulate autoreceptors and in this way assess the separate and combined effects of reduced DA and 5-HT activity upon spontaneous and cocaine induced locomotor behavior. Two separate experiments were conducted. In the first experiment, separate groups of rats (N=10) were tested with either saline, 8OH, APO or 8OH plus APO (0.01, 0.025, 0.05 mg/kg). At 0.05 mg/kg, 8OH and APO induced similar dose related decreases (up to approximately 50%) in locomotor activity. The combined 8OH plus APO treatment induced dose-related decreases in locomotion (approximately 90%). At the 0.05 mg/kg dose level, the drug treatments given separately blocked cocaine induced increases in activity and the 8OH and APO inhibitory effects were again additive. In the second experiment, separate groups (N=10) received saline, 0.05 mg/kg APO, 0.05 mg/kg 8OH or 0.05 mg/kg APO plus 0.05 mg/kg 8OH. As in the first experiment, the 8OH and APO given separately reduced locomotor activity by approximately 50% and when given together, locomotor activity was virtually eliminated (reduced 80-90%). When the combined APO/8OH group also received the 5-HT(1A) antagonist, WAY 100635 (0.05 mg/kg), the effect on activity was equivalent to 0.05 mg/kg APO alone. Ex vivo neurochemical measurement of dopamine (DA) and serotonin (5-HT) metabolism confirmed that the APO decreased DA turnover, 8OH decreased 5-HT turnover and the combined treatment reduced both the DA and 5-HT turnover. Thus, for both spontaneous and cocaine induced locomotor behavior,

the low dose 8OH and APO treatments suppressed locomotor activity and these effects were additive. These findings indicate that DA and 5-HT systems contribute separately to motoric activation. These results suggest that it is important to consider both DA and 5-HT contributions to disorders of motoric impoverishment such as Parkinson's disease as well as to hyperkinetic states such as those induced by stimulant drugs.

Drugs Today (Barc). 2004 Jan;40(1):41-54. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Clinical use of sibutramine.** Ryan DH. Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana 70808, USA. ryandh@pbrc.edu PMID: 14988769 [PubMed - indexed for MEDLINE]

Since obesity is a chronic disorder, a long-term approach is essential, and modern obesity pharmacotherapy means medicating as an adjunct to diet and physical activity not only to achieve weight loss, but also to maintain it. Sibutramine is a US Food and Drug Administration- and European Committee for Proprietary Medicinal Products-approved medication with demonstrated efficacy in long-term obesity management. It is a norepinephrine-serotonin reuptake inhibitor and produces weight loss by a dual mechanism: reduction of food intake and increase in energy expenditure. Sibutramine is given once daily in doses ranging from 5-15 mg. The amount of weight lost with sibutramine is related to both the dose of the drug and the intensity of the behavioral therapy component. Sibutramine produces a weight loss from baseline of more than 5% in over 75% of patients who are prescribed 15 mg daily, and it produces weight loss that averages 5-8% from baseline, independently of the behavioral approach. Weight loss with sibutramine is associated with improvement in waist circumference, lipids, glycemic control, uric acid and health-related quality of life. Sibutramine use is associated with small increases in mean resting blood pressure, but the individual response is variable and not all patients will have blood pressure increases. The drug is also associated with small increases in mean heart rate and should therefore not be used in patients with a history of cardiac arrhythmia. Because it is a serotonin and norepinephrine reuptake inhibitor, sibutramine should not be used with monoamine oxidase inhibitors or noradrenergic agents, and caution is advised in prescribing sibutramine to patients on selective serotonin reuptake inhibitor antidepressants. Given the growing appreciation for the health benefits that can be achieved with even a relatively small weight loss, physicians must become adept in office approaches to achieve modest weight loss. Sibutramine is a useful adjunct to diet and physical activity approaches and can help selected patients achieve and maintain weight loss with concomitant health benefits.

Publication Types:

- Review
- Review, Tutorial

Exp Physiol. 2002 Mar;87(2):215-26. Department of Biomedical Sciences, University Medical School, Aberdeen AB25 2ZD, UK. **Hyperprolactinaemia during prolonged exercise in the heat: evidence for a centrally mediated component of fatigue in trained cyclists.** Pitsiladis YP, Strachan AT, Davidson I, Maughan RJ. PMID: 11856966 [PubMed - indexed for MEDLINE]

Several lines of evidence suggest that central serotonergic neurons may mediate fatigue signals during prolonged exercise. In this study we examined the effects of diet and ambient temperature on peripheral modulators and indices of serotonergic function and their relationship to exercise performance. Six well-trained cyclists participated, in randomised order, in two diet and exercise regimens each lasting 8 days and comprising four cycle tests to exhaustion at 70 % of maximum oxygen uptake. On days 1 and 5, subjects exercised to exhaustion to deplete muscle glycogen. For

3 days after the first depletion trial a diet providing 10 % of energy in the form of carbohydrate (CHO) was consumed (low CHO), and for 3 days after the second depletion trial a diet providing 80 % (high CHO) of energy as CHO was consumed, and each diet was followed by a performance trial at the same ambient temperature, either 10 degrees C or 30 degrees C (days 4 and 8). This schedule was repeated after 1 week, but performance trials were carried out at the other ambient temperature. In the cold, cycling time increased ($P < 0.01$) from 89.2 (78.0-129.5) min (median (range)) in the low CHO trial to 158.2 (116.9-165.6) min in the high CHO trial. In the heat, cycling time increased from 44.0 (31.8-51.4) min in the low CHO trial to 53.2 (50.2-82.2) min on the high CHO trial ($P = 0.02$). The serum prolactin (Prl) concentration was higher at exhaustion during the two trials in the heat than in the two trials in the cold. Serum Prl levels were unrelated to the purported peripheral modulators of serotonergic function (plasma concentrations of total tryptophan (Trp), free Trp, branched-chain amino acids (BCAAs), free Trp/BCAA ratio and total Trp/BCAA ratio) but were significantly related to the rectal temperatures measured during the two trials in the heat. This finding provides indirect evidence that the serotonergic system may be involved in fatigue during exercise under conditions of heat stress.

Neuroscience 2001;103(3):703-11 **Gene expression of catecholamine biosynthetic enzymes following exercise: modulation by age.** Tumer N, Demirel HA, Serova L, Sabban EL, Broxson CS, Powers CK

Both age and exercise training are associated with tissue specific alterations in the catecholaminergic system. We examined the effect of short-term exercise training on tyrosine hydroxylase and dopamine beta-hydroxylase gene expression in adrenals and specific brain regions with aging. In addition, we examined activator protein-1 and cyclic AMP response element transcription factor binding activity in the adrenal medulla. Male, six- and 24-month-old F-344 rats were exercised by treadmill running for five consecutive days. One group was killed immediately and a second group was killed 2h after the last training session. Exercise significantly elevated tyrosine hydroxylase messenger RNA equally in adrenals of both young and old rats. Training had no effect on dopamine beta-hydroxylase messenger RNA in adrenals of young, but levels were elevated in old rats. Binding activities of both activator protein-1 and cyclic AMP response element binding protein were diminished with age in the adrenal medulla. Exercise training had no significant effect on the binding activity of cyclic AMP response element binding protein in either young or old animals, whereas activator protein-1 binding activity increased equally in young and old animals. Exercise training revealed divergent changes in tyrosine hydroxylase messenger RNA in brain catecholaminergic neurons. In the locus coeruleus and the ventral tegmental areas, training elevated tyrosine hydroxylase messenger RNA levels only in young rats. In the substantia nigra, there was no change in young, but a 45% increase in tyrosine hydroxylase messenger RNA in old rats. In the ventral tegmental area, training increased tyrosine hydroxylase gene expression 80% in young but not in old rats. These results indicate that short-term exercise training increases tyrosine hydroxylase messenger RNA levels in young animals in the adrenals, the locus coeruleus and the ventral tegmental area. The responses for exercise training of aged animals differed from the young in brain noradrenergic and dopaminergic nuclei, especially in the substantia nigra, and to some extent in the locus coeruleus and the ventral tegmental area.

Amino Acids 2001;20(1):35-47 **Influence of exercise on serotonergic neuromodulation in the brain.** Weicker H, Struder HK. Department of Sports Medicine, University of Heidelberg, Federal Republic of Germany.

Implications of exercise on serotonergic neuromodulation in the brain have been investigated in two studies. Acute paroxetine (selective serotonin (5-HT) reuptake inhibitor) administration to

endurance athletes, who performed a cycle ergometer test to exhaustion at moderate intensity, reduced time to exhaustion and post exercise cognitive performance in comparison to trials with placebo or BCAA administration. Furthermore, during a three-week moderate endurance training of sedentary males baseline values of Bmax of 5-HT transporters (5-HTT) and 5-HT_{2A} receptors (5-HT_{2A}R) on isolated platelet membranes increased while plasma prolactin (PRL) concentrations decreased as well as mood and physical efficiency improved. In contrast, after an excessive training program over four weeks, well-trained endurance athletes showed no change of Bmax of 5-HTT, but a decline of 5-HT_{2A}R density and an increase in basal plasma PRL concentration. Mood was impaired and central fatigue increased. Thus, the impact of exercise on 5-HT neurotransmission may depend on training state of athletes and extent of exertion. The theoretical background of the implication of exercise and the effect of long lasting exhaustive exercise in athletes on mental and physical efficiency or central fatigue are evaluated. The significance of the primary disturbance of central neuromodulation and dysfunction of 5-HTT, 5-HT receptor subtypes and the phosphoinositol signal transduction as well as the limited modulation capacity of the 5-HT system in overstrain are also addressed.

J Sports Med Phys Fitness 2001 Mar;41(1):95-100 **Postexercise proteinuria in humans and its adrenergic component.** Poortmans JR, Haggemacher C, Vanderstraeten J. Chimie Physiologique, Institut Supérieur d'Éducation Physique et de Kinesithérapie, Université Libre de Bruxelles, Bruxelles, Belgium.

BACKGROUND: Postexercise proteinuria is a common phenomenon depending on hypothetical mechanisms such as the hemodynamic system and its sympathetic component. To test this hypothesis we administered an α_2 -adrenergic agonist (clonidine) in order to reduce the catecholamine response during exercise. **METHODS:** Clonidine (300 mg) and a placebo, one week apart, were administered randomly to nine healthy male subjects (23 yrs age) two hours prior to a maximal exercise test on bicycle ergometer. Blood samples and urine collections were obtained at rest and after exercise. Lactate in plasma, creatinine and albumin in plasma and urine were assayed and their clearances were calculated. **RESULTS:** Postexercise lactate was identical under placebo and clonidine administration (10.11.0 versus 11.31.7 mmol.⁻¹). It was observed that the clonidine treatment induced a lesser postexercise proteinuria (21328 versus 29855 mg.min⁻¹) and albuminuria (71.816.3 versus 116.834.2 mg.min⁻¹) when compared to the placebo test. The postexercise renal clearance of albumin did show a reduction of 40% under the influence of clonidine. **CONCLUSIONS:** It may be argued that the catecholamines are partially acting on the mechanisms of the enhanced permeability of the glomerular membrane induced by strenuous exercise.

Acta Physiol Scand 2000 Nov;170(3):211-6 **Endurance training in Wistar rats decreases receptor sensitivity to a serotonin agonist.** Dwyer D, Browning J. School of Health Science, Griffith University, Gold Coast, Australia.

There is mounting evidence that increased brain serotonin during exercise is associated with the onset of CNS-mediated fatigue. Serotonin receptor sensitivity is likely to be an important determinant of this fatigue. Alterations in brain serotonin receptor sensitivity were examined in Wistar rats throughout six weeks of endurance training, running on a treadmill four times a week with two exercise tests per week to exhaustion. Receptor sensitivity was determined indirectly as the reduction in exercise time in response to a dose of a serotonin (1A) agonist, m-chlorophenylpiperazine (m-CPP). The two groups of controls were used to examine (i) the effect of the injection per se on exercise performance and (ii) changes in serotonin receptor sensitivity associated with maturation. In the test group, undrugged exercise performance significantly improved by 47% after six weeks of training (4518 \pm 729 to 6640 \pm 903 s, P=0.01). Drugged

exercise performance also increased significantly from week one to week six (306 +/- 69-712 +/- 192 s, P = 0.04). Control group results indicated that the dose of m-CPP alone caused fatigue during exercise tests and that maturation was not responsible for any decrease in receptor sensitivity. Improved resistance to the fatiguing effects of the serotonin agonist suggests desensitization of central serotonin receptors, probably the 5-HT1A receptors. Endurance training appears to stimulate an adaptive response to the fatiguing effects of increased brain serotonin, which may enhance endurance exercise performance.

Psychosom Med 2000 Nov;62(6):866-72 Dynamic exercise discloses different time-related responses in stress hormones. de Vries WR, Bernardis NT, de Rooij MH, Koppeschaar HP Department of Medical Physiology and Sports Medicine, University Medical Center Utrecht, The Netherlands.

OBJECTIVE: Responses to stressful events are generally regarded as reactions of the organism to accommodate to or compensate for stress. This reaction is classically described as an activation of the sympathoadrenal system and the hypothalamic-pituitary-adrenocortical (HPA) axis. Activation of the release of growth hormone and prolactin in blood also occurs during various types of stress. Assuming that the stress response is a neuroendocrine mechanism that occurs in anticipation of physical exercise, we investigated whether an incremental exercise protocol can be used as a model stressor to disclose a distinct pattern of activation in these hormonal systems, which would support the notion that these systems have different roles in preparing the organism for physical activity and recovery. Moreover, such a model may help improve our understanding of the endocrine expressions of psychological stress. **METHODS:** After an overnight fast, eight healthy men (age 19-26 years) cycled at 40, 60, 80, and 100% of the power output at VO₂max in successive time blocks of 10 minutes each up to exhaustion. Venous blood was sampled immediately before exercise, at the end of each block, and during the recovery phase 5 and 30 minutes after exercise. Plasma adrenalin and noradrenalin were measured by high-performance liquid chromatography; plasma adrenocorticotrophic hormone, beta-endorphin, cortisol, growth hormone, and prolactin were measured by specific immunoassays. Heart rate and levels of blood lactate and adrenalin were measured as markers of workload-related responses. **RESULTS:** Results showed that increases in heart rate, lactate, adrenalin, noradrenalin, and growth hormone reflected the relative workload, in contrast to increases in adrenocorticotrophic hormone, beta endorphin, and prolactin, which were observed only after exercise reached an intensity of 80% VO₂max. Increases in cortisol were found just after exhaustion. The delayed response of cortisol may be initiated by a drop in blood glucose levels but may also be considered preparatory to vigorous muscular effort and protective against tissue damage. **CONCLUSIONS:** Measurement of the cumulative response to exercise shows that activation of stress hormones occurs at different time points, supporting the notion that these hormones have different roles in preparing the organism for physical activity and recovery: i.e., workload- and effort-related adaptation on one hand and protection against disturbed homeostasis on the other. The delayed response of the HPA axis during incremental exercise contrasts with the nondelayed HPA axis response observed during psychological stress and points to involvement of different neurobiological and cognitive emotional mechanisms.

Can J Appl Physiol 1999 Dec;24(6):524-37 Acute hormonal responses to a single bout of heavy resistance exercise in trained power lifters and untrained men. Kraemer WJ, Fleck SJ, Maresh CM, Ratamess NA, Gordon SE, Goetz KL, Harman EA, Frykman PN, Volek JS, Mazzetti SA, Fry AC, Marchitelli LJ, Patton JF. Human Performance Laboratory, Ball State University, Muncie, IN 47306, USA.

The purpose of this study was to investigate the acute responses of both stress and fluid regulatory hormones to a single bout of resistance exercise in both trained and untrained men. Seven

competitive power lifters (PL) and 12 untrained subjects (UT) performed one set of the leg press exercise to exhaustion at 80% of their respective one-repetition maximum. Blood samples were obtained twice prior to exercise (at P1 and P2), immediately postexercise (IP), and at five minutes postexercise (5PE). Compared to P1 and P2, plasma epinephrine, norepinephrine, dopamine, atrial peptide, osmolality, and blood lactic acid increased significantly ($p < \text{or} = 0.05$) at IP. Plasma epinephrine, norepinephrine, atrial peptide, and blood lactic acid concentrations remained elevated at 5PE compared to P1 and P2. Plasma renin activity and angiotensin II were significantly elevated at 5PE compared to P1, P2, and IP, and this increase was significantly greater in PL compared to UT at 5PE. These data indicate that an acute bout of resistance exercise dramatically affects secretion of stress and fluid regulatory hormones.

Eur J Appl Physiol Occup Physiol 1999 Mar;79(4):318-24 **Effect of acute and chronic exercise on plasma amino acids and prolactin concentrations and on [3H]ketanserin binding to serotonin2A receptors on human platelets.** Struder HK, Hollmann W, Platen P, Wostmann R, Weicker H, Molderings GJ. Institute of Sports Games, German Sport University, Cologne.

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been shown to modulate various physiological and psychological functions such as fatigue. Altered regulation of the serotonergic system has been suggested to play a role in response to exercise stress. In the present study, the influence was investigated of acute endurance exercise and short-term increase in the amount of training on the concentrations of the 5-HT precursor tryptophan (TRP), of prolactin (PRL) and of branched-chain amino acids (BCAA) in the blood, as well as on the binding of [3H]ketanserin to the serotonin-2A (5-HT_{2A}) receptors on platelets. Nine healthy endurance-trained men were tested the day before (I) and after (II) a nine-day training programme. Samples of venous blood were drawn after an overnight fast and following 5 h of cycling. Fasted and post-exercise plasma concentrations of free TRP, BCAA and free TRP:BCAA ratio did not differ between I and II. A significant decrease of plasma BCAA ($P < 0.01$) and significant augmentations of plasma free TRP, free TRP:BCAA ratio and PRL ($P < 0.01$) were found post-exercise. The increase in plasma PRL was smaller in II compared with I. Acute endurance exercise reduced the density of platelet 5-HT_{2A} receptor [3H]ketanserin binding sites at I and II ($P < 0.05$). The basal density of the binding sites and the affinity of [3H]ketanserin for these binding sites were unaffected by an increase in the amount of training. The present results support the hypothesis that acute endurance exercise may increase 5-HT availability. This was reflected in the periphery by increased concentration of the 5-HT precursor free TRP, by increased plasma PRL concentration, and by a reduction of 5-HT_{2A} receptors on platelets. It remains to be resolved whether these alterations in the periphery occur in parallel with an increase in the availability of 5-HT in the brain.

Strachan AT, Maughan RJ **"Platelet serotonin transporter density and related parameters in endurance-trained and sedentary male subjects."** Acta Physiol Scand 1998 Jun; 163(2): 165-71 Department of Clinical Biochemistry, Aberdeen Royal, Hospitals Trust, Foresterhill, UK.

A number of peripheral indices of serotonergic function were examined in endurance-trained (ET) and sedentary males using the blood platelet as a model of the serotonergic neurone. The aim of the study was to investigate possible involvement and adaptation of the central serotonergic system in exercise-induced fatigue. The [3H] paroxetine-defined density of platelet serotonin transporters, platelet serotonin content and the plasma concentration of amino acids were determined in 10 ET and eight sedentary males. The mean (standard deviation) density of the serotonin transporter in the platelet membranes of the ET subjects was greater [1237 (182) fmol mg protein⁻¹] than that of the sedentary subjects [910 (119) fmol mg protein⁻¹; $P = 0.013$]. No

difference ($P = 0.51$) could be seen between the median (range) platelet serotonin content of the ET subjects [0.98 (0.37-3.04) nmol platelet-10] and that of the sedentary subjects [0.82 (0.18-1.49) nmol platelet-10]. The platelet poor plasma concentrations of tryptophan and tyrosine were lower in the ET subjects ($P = 0.028$ and 0.015 , respectively). The present study suggests that the platelet membrane of the ET subjects has a greater density of the serotonin transporter and that this is inversely related to the circulating concentration of the serotonin precursor, tryptophan. It remains to be resolved whether the increase in serotonin transporter density in the platelet membrane of ET subjects is reflected centrally and whether the ET platelet population may be sufficiently different from that of sedentary individuals to alter serotonin transporter density.

Struder HK, Hollmann W, Platen P, Donike M, Gotzmann A, Weber K **“Influence of paroxetine, branched-chain amino acids and tyrosine on neuroendocrine system responses and fatigue in humans.”** Horm Metab Res 1998 Apr; 30(4): 188-94 Institute of Sports Games, German Sport University, Koln.

Effects of a serotonin re-uptake inhibitor and oral amino acid supplementations on physical and mental performance as well as neuroendocrine variables were investigated. 10 male subjects cycled in four trials until exhaustion. Participants ingested a placebo in trial (T) I, 20 mg paroxetine in T II, 21 g branched-chain amino acids (BCAA) in T III and 20g tyrosine (TYR) in T IV. Heart rate, capillary lactate, plasma insulin, free fatty acids, glucose, serotonin and beta-endorphin did not differ in trials. Plasma ammonia increments during exercise were higher in T III. Plasma BCAA in T III and plasma TYR in T IV were increased after 30 min of exercise according to the supplemented substances. In contrast to all other trials, the ratio of plasma free TRP/BCAA did not increase in T III. Plasma TYR/BCAA was augmented in T IV and decreased in T III after 30 min of exercise, whereas it did not change in T I and II. Plasma prolactin (PRL), growth hormone, cortisol, adrenocorticotrophic hormone, norepinephrine and epinephrine increased during all trials. Plasma PRL increments were higher in T IV. Exhaustion was reached earlier in T II. No significant differences were found between other trials. Drive during psychometric testing subsequent to exercise was improved in T III and IV. The results indicate that fatigue during endurance exercise was increased by pharmacological augmentation of the brain serotonergic activity. However, a reduction of 5-HT synthesis via BCAA supplementation did not affect physical fatigue. TYR administration did not alter physical performance either although plasma PRL increments suggest that changes in the monoaminergic system were induced. Precaution is necessary before assuming an ergogenic value of amino acids.

Eur J Clin Nutr. 1998 Apr;52(4):300-7. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Exercise in dietary restrained women: no effect on energy intake but change in hedonic ratings.** Lluch A, King NA, Blundell JE. BioPsychology Group, School of Psychology, University of Leeds, UK. PMID: 9578343 [PubMed - indexed for MEDLINE]

OBJECTIVES: To investigate the short-term effects (one day) of exercise and diet composition on appetite control in restrained females. **DESIGN:** 2x2 repeated measures design, with exercise and lunch type used as the repeated factors. **SETTING:** The Human Appetite Research Unit at Leeds University Psychology Department. **SUBJECTS:** Twelve dietary restrained females, normal weight and regular exercisers **INTERVENTIONS:** A control (rest) and a bout of high intensity exercise (cycling 50 min., 70% VO_2 max.) was followed by a free-selection lunch comprising high-fat (HF) or low-fat (LF) foods. Hunger and heart rate profiles were tracked. Energy Intake (EI) was monitored in the laboratory throughout the day. Post-meal hedonic ratings were completed after lunch and dinner. **RESULTS:** There was a significant effect of lunch type (HF vs LF) on EI following exercise and rest ($P < 0.001$) and on total 24 h EI ($P < 0.05$): EI increased

during both HF conditions compared to the LF. A main effect of exercise on tastiness and pleasantness ($P < 0.05$) of the LF foods served at lunch was found. However, there was no effect of exercise on hunger, weight or energy value of food eaten. **CONCLUSIONS:** Exercise raises the perceived pleasantness of foods in dietary restrained women, but does not increase the drive to eat within 8 h of the cessation of exercise. The combination of physical activity and a low-fat diet could be used advantageously to control appetite, prevent overconsumption and protect against the development of obesity.

Acta Physiol Scand 1997 Jan; 159(1): 41-9 **“Influence of ingesting a solution of branched-chain amino acids on perceived exertion during exercise.”** Blomstrand E, Hassmen P, Ek S, Ekblom B, Newsholme EA Pripps Bryggerier, Research Laboratories, Stockholm, Sweden.

On two occasions, seven male endurance-trained cyclists performed exhaustive exercise on a cycle ergometer in the morning after they had performed a bout of exercise the preceding evening in an attempt to lower the muscle glycogen stores. The subjects exercised at a work rate corresponding to approximately 70% of their maximal oxygen uptake for 60 min, followed by another 20 min of maximal exercise. During exercise the subjects were given either a solution of branched-chain amino acids (BCAAs) or flavoured water (placebo). Every 10 min during exercise the subjects rated their perceived exertion and mental fatigue on two different Borg scales. During the 60 min exercise at a given work rate the subjects' ratings of perceived exertion when they were given BCAAs were 7% lower, and their ratings of mental fatigue were 15% lower than when they were given placebo. In addition, the performance in the colour task of Stroops Colour Word Test performed after exercise was improved when BCAAs had been ingested during exercise, compared with the results from the placebo trial. There was no difference in the physical performance between the two trials measured as the amount of work done during the last 20 min of exercise when the subjects performed at their maximum. The plasma concentration ratio of free tryptophan/BCAAs, which increased by 45% during exercise and by 150% 5 min after exercise in the placebo trial, remained unchanged or even decreased when BCAAs were ingested.

J Sports Sci 1995 Summer;13 Spec No:S49-53 **Central and peripheral factors in fatigue.** Davis JM. Department of Exercise Science, University of South Carolina, Columbia, SC 29208, USA.

The causes of fatigue during muscular exercise include factors that reside in the brain (central mechanisms) as well as the muscles themselves (peripheral mechanisms). Central fatigue is largely unexplored, but there is increasing evidence that increased brain serotonin (5-HT) can lead to central (mental) fatigue, thereby causing a deterioration in sport and exercise performance. Although there are also strong theoretical grounds for a beneficial role of nutrition in delaying central fatigue, the data are much more tenuous. Dietary supplementation with branched-chain amino acids (BCAA) in low doses produces small and probably inconsequential effects on peripheral markers of brain 5-HT synthesis (plasma free tryptophan/BCAA), whereas larger doses are likely to be unpalatable, reduce the absorption of water in the gut, and may increase potentially toxic ammonia concentrations in the plasma. Alternatively, carbohydrate supplementation results in large reductions in plasma free tryptophan/BCAA and exercise time to fatigue is significantly longer, but it is difficult to distinguish between the effects of carbohydrate feedings on central fatigue mechanisms and the well-established beneficial effects of carbohydrate supplements on the contracting muscle. These data support the exciting possibility that relationships exist among nutrition, brain neurochemistry and sport performance. However, while the evidence is intriguing and makes good intuitive sense, our knowledge in this area is rudimentary at best.

Adv Exp Med Biol 1995;384:315-20 **Tryptophan, 5-hydroxytryptamine and a possible explanation for central fatigue.** Newsholme EA, Blomstrand E. Department of Biochemistry, University of Oxford, United Kingdom.

In prolonged exercise the plasma level of branched-chain amino acids (BCAA) may fall and that of fatty acid increases: the latter increases the free tryptophan level, so that the plasma concentration ratio, free tryptophan/BCAA may increase leading to higher levels of tryptophan and therefore of 5-hydroxytryptamine (5-HT) in brain. The latter increases the activity of some 5HT neurons in the brain which can cause sleep and which could, therefore, increase the mental effort necessary to maintain athletic activity. Drinks containing branched-chain amino acids should restore vigor to athletes whose performance is depressed by an excess of cerebral 5-HT. Recent work suggests that intake of branched-chain amino acids may improve performance in slower runners in the marathon and decrease perceived physical and mental exertion in laboratory experiments. This suggestion is supported by pharmacological manipulations that result in either increased or decreased physical performance.

Soares J Naffah-Mazzacoratti MG Cavalheiro EA **“Increased serotonin levels in physically trained men.”** Braz J Med Biol Res (1994 Jul) 27(7): 1635-8

It has been postulated that exercise training influences monoaminergic systems. The purpose of the present study was to determine the basal level of serum serotonin (5HT) in track and field-trained men (N = 15) and in untrained subjects matched by age, weight and height (N = 15). Serum serotonin levels were determined in blood drawn into dry tubes after a 12-h fast by high performance liquid chromatography utilizing electrochemical detection. Mean (+/- SD) serum serotonin levels were: 141.32 +/- 38.77 ng/ml for trained subjects and 97.77 +/- 30.53 ng/ml for untrained subjects (P < 0.01, Student t-test). These data show that basal serum serotonin levels are increased by exercise training.

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Diet Abstracts:

Brain Res Mol Brain Res. 2004 Aug 23;127(1-2):39-47. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Differential expression of 5-HT(2A) and 5-HT(2C) receptor mRNAs in mice prone, or resistant, to chronic high-fat diet-induced obesity.** Huang XF, Han M, Storlien LH. Molecular Neurobiology Laboratory, Department of Biomedical Science, University of Wollongong, Wollongong, NSW 2522, Australia. PMID: 15306119 [PubMed -in process]

The present study examined the levels of 5-HT(2A) and 5-HT(2C) (2A and 2C receptors of 5hydroxytryptamine; serotonin) receptor messenger RNA (mRNA) expressions in the brain of chronic high-fat diet-induced obese (DIO) and obese-resistant (DR) mice. Thirty-one mice were used in this study. Twenty-four mice were fed with a high-fat diet (HF: 40% of calories from fat) for 4 weeks and then classified as the DIO (n=8) or DR (n=8) mice according to the highest and lowest body weight (BW) gainers. Seven mice were placed on a low-fat diet (LF: 10% of calories from fat) and were used as controls. After 20 weeks of feeding, the visceral fat accumulation was 620+/-42 mg in the DIO group versus 198+/-89 mg in the DR and 84+/-18 mg in the LF groups. Using quantitative in situ hybridization techniques, levels of 2A and 2C serotonin (5-HT) receptor mRNAs were measured in multiple brain sections of mice from the three groups. Most regions did not differ between groups but, importantly, the DIO mice had a significantly higher level of 5-HT(2A) receptor mRNA expression in the olfactory nucleus (Olf) compared to the DR and LF mice (+30% and +37%, respectively). The levels of Olf 5-HT(2A) receptor mRNA expression

were related to body fat mass. The level of 5-HT(2C) mRNA receptor expression in the ventromedial hypothalamic (VMH) nucleus was 40% higher in the DIO mice than in the LF mice. Furthermore, the 5-HT(2C) receptor mRNA expression in the posterodorsal part of the medial amygdaloid (MePD) nucleus was 25% higher in the DIO mice than in the DR mice. The level of VMH 5-HT(2C) receptor mRNA expression was correlated with body fat mass. In conclusion, this study has demonstrated differentially regulated levels of the 5-HT(2A) and 5-HT(2C) receptor mRNA expressions in the specific brain regions of the DIO and DR mice. It provides neural anatomical bases that the 5-HT(2C) receptors positively influence satiety center (VMH) while the 5-HT(2A) receptor regulates olfactory sensory effects. The findings also assist us to understand the role of these receptors in mice susceptible or resistant to diet-induced obesity.

N Neurotoxicol Teratol. 2004 Jul-Aug;26(4):599-605. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Effects of 2,4-dichlorophenoxyacetic acid exposure on dopamine D2-like receptors in rat brain.** Bortolozzi AA, Evangelista De Duffard AM, Duffard RO, Antonelli MC. Laboratorio de Toxicologia Experimental, Facultad de Ciencias Bioquimicas y Farmaceuticas, UNR, Suipacha 531, Rosario Province, Santa Fe 2.000, Argentina. PMID: 15203183 [PubMed - in process]

2,4-Dichlorophenoxyacetic acid (2,4-D), a worldwide-used herbicide, has been associated with a range of adverse health effects on humans and different animal species. Although the mechanism of 2,4-D neurotoxicity remains unknown, we had previously reported changes in various neurotransmitter systems, such as serotonin (5-HT) and dopamine (DA), which were proposed to mediate some of the behavioral effects in rats. In the present work, we examined the impact of 2,4-D exposure on the ontogeny of dopaminergic D2-type receptors in prefrontal cortex (PFC), striatum (CPu), hippocampus (H) and cerebellum (Cer). Pregnant rats were orally exposed to 70 mg/kg/day of 2,4-D from gestation day (GD) 16 to postpartum day 23. After weaning, the pups were assigned to one of the two subgroups: T1 [fed with untreated diet until postnatal day, (PD) 90] and T2 [maintained with 2,4-D diet until PD 90]. Five to eight pups per age and sex were sacrificed at 6, 15, 30, 45 or 90 days of age for membrane receptor binding assays employing [³H]nemonapride. Subchronic 2,4-D exposure (T2 group) increased DA D2-type receptor around 40% in CPu. In addition, DA D2-type receptor levels also increased in PFC (15 and 30 days) and Cer (30 and 90 days). Sex-dependent differences in D2 receptors were observed with T2 female rats being more affected than T2 male rats. When the herbicide treatment was interrupted after weaning (T1 group), DA D2-type receptor density was apparently recovered and stabilized to control level. These findings suggest a reversible vulnerability of D2-type receptors to 2,4-D exposure. Regional increases of D2-type receptor density may explain certain behaviors reported early by us, such as catalepsy and right-turning preference in rats exposed to 2,4-D. Copyright 2004 Elsevier Inc.

J Psychiatr Res. 2004 Jul-Aug;38(4):445-50. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Effects of fluoxetine on ethanol withdrawal syndrome in rats.** Uzbay IT, Sag Lam E, Kayir H, Celik T, Beyazyurek M. Department of Medical Pharmacology, Faculty of Medicine, Psychopharmacology Research Unit, Gulhane Military Medical Academy, Etlik, 06018 PMID: 15203297 [PubMed - in process] Ankara, Turkey. tuzbay@gata.edu

The present study was designed to investigate the effects of fluoxetine, a selective serotonin reuptake inhibitor, on ethanol withdrawal syndrome in rats. Adult male Wistar rats (218-255 g) were subjects. Ethanol (7.2%, v/v) was given to rats by a liquid diet for 21 days. Control rats were pair fed an isocaloric liquid diet containing sucrose as a caloric substitute to ethanol. Fluoxetine (2.5, 5 and 10 mg/kg) and saline were injected to rats intraperitoneally just before ethanol

withdrawal. After 2nd, 4th and 6th hour of ethanol withdrawal, rats were observed for 5 min, and withdrawal signs that included locomotor hyperactivity, agitation, stereotyped behavior, wet dog shakes and tremor were recorded or rated. A second series of injections was given at 6 h after the first one, and subjects were then tested for audiogenic seizures. Fluoxetine produced some dose-dependent and significant inhibitory effects on all the signs of ethanol withdrawal during ethanol withdrawal period. Our results suggest that acute fluoxetine treatment has some beneficial effects on ethanol withdrawal in rats. Thus, this drug may be useful for treatment of ethanol withdrawal syndrome.

J Psychiatry Neurosci. 2004 Jul;29(4):252-65. National Center for Biotechnology Information) at the U.S. National Library of Medicine. **The therapeutic role of 5-HT(1A) and 5-HT(2A) receptors in depression.** Celada P, Puig M, Amargos-Bosch M, Adell A, Artigas F Department of Neurochemistry, Institut d'Investigacions Biomediques de Barcelona, Consejo Superior de Investigaciones Cientificas (Institut d'Investigacions Biomediques August Pi i Sunyer), Barcelona, Spain. PMID: 15309042 [PubMed - in process]

The selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant drugs, because they are well tolerated and have no severe side effects. They rapidly block serotonin (5-HT) reuptake, yet the onset of their therapeutic action requires weeks of treatment. This delay is the result of presynaptic and postsynaptic adaptive mechanisms secondary to reuptake inhibition. The prevention of a negative feedback mechanism operating at the 5-HT autoreceptor level enhances the neurochemical and clinical effects of SSRIs. The blockade of 5-HT(2A) receptors also seems to improve the clinical effects of SSRIs. These receptors are located postsynaptically to 5-HT axons, mainly in the neocortex. Pyramidal neurons in the prefrontal cortex are particularly enriched in 5-HT(2A) receptors. Their blockade may affect the function of prefrontal-subcortical circuits, an effect that probably underlies the beneficial effects of the addition of atypical antipsychotic drugs, which are 5-HT(2A) receptor antagonists, to SSRIs in treatment-resistant patients.

Alcohol Clin Exp Res. 2004 Jun;28(6):941-8. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Prenatal alcohol exposure causes long-term serotonin neuron deficit in mice.** Sari Y, Zhou FC. Indiana University School of Medicine, Department of Anatomy and Cell Biology, Indianapolis, Indiana 46202, USA. PMID: 15201637 [PubMed - in process]

BACKGROUND: Previous work from this laboratory showed that prenatal alcohol exposure at approximately 100 mg/dl from embryonic day (E)7 to early midgestation reduced the number and retarded the migration of serotonin (5-HT) neurons in the raphe nuclei in C57BL/6 mice. In this study, we report that the deficit of 5-HT neurons found in midgestation persisted on E18 and into young adulthood. **METHODS:** Pregnant dams were treated from E7 to E18 in three groups--(1) the alcohol group, fed with liquid diet with 25% ethanol-derived calories; (2) the isocaloric pair-fed group; and (3) the chow group for analysis of concentrations of active caspase-3--to study apoptosis at E18 in the brainstem and the number of 5-HT neurons at E18 and postnatal day 45. The concentrations of active caspase-3 were determined by using a colorimetric assay, and the 5HT neurons were determined by immunocytochemistry. **RESULTS:** Prenatal alcohol exposure increased the concentration of active caspase-3 in the brainstem and caused reductions in brain weight by 20% and in the total number of 5-HT-immunostaining neurons in the dorsal and median raphe nuclei by 20% at E18 as compared with those of the pair-fed and chow controls. Continuous observation from prenatal to postnatal

stages showed that the reduction of 5-HT-immunostaining neurons in the dorsal and median raphe nuclei persisted in the young adult stage. CONCLUSIONS: Upon prenatal alcohol exposure, an increased concentration of active caspase-3 and a decreased number of 5-HT-immunostaining neurons in the brainstem were observed at E18. The decreased number of 5-HT neurons persisted to the young adult stage of postnatal day 45. This suggests that ethanol has a long-lasting effect on 5-HT deficit. A fetal alcohol exposure-rendered lasting deficit of 5-HT and other transmitter systems may underlie the neuropsychiatric deficits in fetal alcohol spectrum disorder. Copyright 2004 Research Society on Alcoholism

Eur J Clin Nutr. 2004 Apr;58(4):637-42. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Rapid carbohydrate digestion rate produced lesser short-term satiety in obese preschool children.** Alvina M, Araya H. Department of Nutrition, Faculty of Medicine, University of Chile, Santiago, Chile. malvina@machi.med.uchile.cl PMID: 15042132 [PubMed -indexed for MEDLINE]

OBJECTIVE: To examine whether high carbohydrate meals with different carbohydrate digestion rates have an effect on the short-term satiety in normal and obese preschool children. SUBJECTS AND SETTING: In total, 48 children of both gender, 24 normal and 24 obese, according to body mass index, aged between 3 and 6 y, were selected from children who were attending to a day-care center where they consumed three meals in the day. INTERVENTIONS: Rapid (potato-based meal) and lente (spaghetti-based meal) carbohydrate digestion rate meal were given at lunch, matching energy intake, carbohydrate, protein and fat levels, and then the preschool children's energy intake at the subsequent mealtime was observed. In this last mealtime, the children received varied types of high-acceptability foods in higher quantities than the normal serving. RESULTS: At lunch, a significant higher energy intake, lesser satiety, was observed in both groups, normal-weight and obese children, when they consumed the potato-based meal. In the subsequent mealtime, a significant effect of carbohydrate digestion rate was demonstrated, but only in obese preschool children, being higher in the meal with rapid digestion rate carbohydrates. CONCLUSIONS: Rapid carbohydrate digestion rate meal produced a significative lesser satiety in normal-weight and obese children. However, only in obese children a significant lesser satiety was observed after consumption of the rapid carbohydrate digestion rate meal, indicating a decreased capacity of energy regulation in obese children. The finding of the present work could provide dietary strategies required for decreasing prevalence in overweight and obesity in preschool children. Publication Types:

Behav Brain Res. 2004 Jan 5;148(1-2):1-10. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Alpha-lactalbumin-enriched diets enhance serotonin release and induce anxiolytic and rewarding effects in the rat.** Orosco M, Rouch C, Beslot F, Feurte S, Regnault A, Dauge V. CNRS UMR 7059, Universite Paris 7, Case 7126, 2 Place Jussieu, 75251 Paris Cedex 05, France. PMID: 14684242 [PubMed - indexed for MEDLINE]

Among food proteins, alpha-lactalbumin (LAC) has the highest ratio of tryptophan (Trp) over its competitor amino acids. Consequently, contrary to casein (CAS), LAC ingestion increases Trp access to the brain leading to enhanced serotonin (5-HT) synthesis. As an index of serotonergic activity, we assessed extracellular 5-HT in response to LAC ingestion, using microdialysis, and performed behavioural tests in rats in order to characterise the suggested improvements of mood observed in humans after ingestion of this protein. Rats were fed with diets enriched either in LAC or CAS as control, acutely (30 min meals) or chronically (3 and 6 days). A 30 min LAC meal significantly increased 5-HT release in the medial hypothalamus. This effect disappeared after 3 and 6 days of diet. The basal premeal 5-HT levels were increasingly enhanced by the LAC diet.

Compared to a CAS meal, LAC increased the percentage of time spent on the open arms of the elevated plus maze and the number of visits to the centre of the open field, suggesting an anxiolytic-like effect. A single LAC meal decreased sucrose consumption, while 3 or 6 days diets enhanced it, reflecting an appetitive and/or rewarding action. In conclusion, LAC ingestion induces anxiolytic-like and rewarding effects possibly related to serotonergic activation. Shifting transiently, the commonly consumed CAS-enriched to LAC-enriched diets may induce beneficial effects on mood.

Int J Eat Disord. 2004 Jan;35(1):16-26. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Clinical trial of sertraline in the treatment of night eating syndrome.** O'Reardon JP, Stunkard AJ, Allison KC. Department of Psychiatry, Weight and Eating Disorders Program, University of Pennsylvania, Philadelphia, 19104, USA. oreardon@mail.med.upenn.edu PMID: 14705153 [PubMed - indexed for MEDLINE]

OBJECTIVE: To test the efficacy of sertraline in the treatment of night eating syndrome.
METHODS: Seventeen patients meeting criteria for night eating syndrome received sertraline in a 12-week open-label, nonblind trial. Outcome was assessed by four primary measures, namely, the number of nocturnal awakenings, the number of ingestions, total daily caloric intake after the evening meal, and an overall rating of change from the Clinical Global Impression of Improvement scale (CGI-I). **RESULTS AND DISCUSSION:** An intent-to-treat analysis revealed highly significant improvements across all four primary outcome measures for all 17 subjects. Five subjects achieved full remission of symptoms (CGI-I score of 1 = very much improved) and lost a significant amount of weight over the course of the study (-4.8 +/- 2.6 kg, $p < .05$). Sertraline, a selective serotonin reuptake inhibitor, may be beneficial in the treatment of night eating syndrome. Copyright 2003 by Wiley Periodicals, Inc. Int J Eat Disord 35: 16-26, 2004.

Publication Types:

- Clinical Trial

Nutr Neurosci. 2003 Oct;6(5):291-9. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Effects of amino acid deficiency on monoamines in the lateral hypothalamus (LH) in rats.** Blevins JE, Teh PS, Wang CX, Gietzen DW. Division of Endocrinology/Metabolism, Department of Veterans Affairs Medical Center, University of Washington, Seattle, WA 91808, USA. jblevin@u.washington.edu PMID: 14609315 [PubMed - indexed for MEDLINE]

Animals decrease intake of an indispensable amino acid deficient diet, due in part to decreased dietary limiting amino acid concentrations within the anterior piriform cortex (APC). In addition to studies supporting a primary role for the APC in this phenomenon, recent studies have shown that the lateral hypothalamus (LH), which receives projections from the APC, also mediates the anorectic response to amino acid deficiency. The neurochemical changes within the LH that accompany the anorexia to amino acid deficiency are unclear. We hypothesized that norepinephrine (NE), dopamine (DA) and serotonin, whose levels are altered in response to amino acid deficiency within the APC, also act within the LH to mediate amino acid deficiency-induced anorexia. We determined that ingestion of an amino acid devoid diet increased concentrations of NE and the serotonin metabolite, 5-hydroxyindoleacetic acid in the LH. The 5-hydroxytryptamine metabolite was increased overall, according to analysis by area under the curve. Individual points reached significance at 130 min; NE was elevated at 170 min. These results suggest that the sustained anorectic response following ingestion of an amino acid devoid diet may be associated with increased activity of the NE and 5-hydroxytryptamine systems in the LH.

Psychopharmacology (Berl). 2003 Aug;169(1):104-7. Epub 2003 Apr 29. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Acute administration of nutritionally sourced tryptophan increases fear recognition.** Attenburrow MJ, Williams C, Odontiadis J, Reed A, Powell J, Cowen PJ, Harmer CJ. University Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX, UK. PMID: 12719963 [PubMed - indexed for MEDLINE]

RATIONALE: The serotonin precursor tryptophan (TRP) has been widely used as a nutritional supplement and antidepressant. Recently, however, the use of TRP has been severely restricted due to its association with the eosinophilic myalgic syndrome, an autoimmune disorder probably caused by ingestion of a contaminant produced in certain TRP manufacturing processes. **OBJECTIVES:** To determine the bioavailability of a nutritional source of TRP obtained from milk protein and to assess whether administration of this material produced neuroendocrine and neuropsychological effects consistent with increased brain serotonin activity. **METHODS:** We studied 24 healthy subjects who ingested approximately 1.8 g of nutritionally-sourced TRP or placebo in a double-blind, parallel group, design. We carried out venous sampling for amino acid and hormone estimation and performed a test of emotional processing using a facial expression recognition task. **RESULTS:** The nutritionally-sourced TRP caused a substantial increase in the availability of TRP in plasma. Relative to placebo the TRP material produced some evidence of an increase in plasma cortisol, and enhanced the perception of fearful and happy facial expressions. **CONCLUSIONS:** A nutritional source of TRP increased the availability of TRP for brain serotonin synthesis and produced endocrine and neuropsychological changes consistent with increased brain serotonin function. The effect of TRP on emotional processing may be relevant to its reported activity in primate studies of social behaviour.

Publication Types:

- . • Clinical Trial
- . • Randomized Controlled Trial

Int J Eat Disord. 2003 Apr;33(3):257-67; discussion 268-70. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Anxiolytic effects of acute tryptophan depletion in anorexia nervosa.** Kaye WH, Barbarich NC, Putnam K, Gendall KA, Fernstrom J, Fernstrom M, McConaha CW, Kishore A. Department of Psychiatry, Anorexia and Bulimia Nervosa Research Module, University of Pittsburgh Medical School, 600 Iroquois Building, 3811 O'Hara Street, Pittsburgh, PA 15213, USA. kayewh@msx.upmc.edu PMID: 12655621 [PubMed - indexed for MEDLINE]

OBJECTIVE: Recent studies have raised the question as to whether a dysregulation of the neurotransmitter serotonin may contribute to the alterations in mood seen in anorexia nervosa (AN). People with AN tend to be anxious, obsessional, perfectionistic, and harm avoidant. These traits are premorbid and persist after recovery. It has been suggested that increased activity of brain serotonin systems could contribute to this pathologic condition. Dieting in AN, which serves to reduce plasma levels of tryptophan (TRP), may serve to reduce symptoms of dysphoric mood. **METHOD:** Fourteen women currently symptomatic with AN (ILL AN), 14 women recovered from AN (REC AN), and 15 healthy control women (CW) underwent acute tryptophan depletion (ATD). Measures of psychological state were self-assessed at baseline and hourly after ATD to determine whether ATD would reduce negative mood. **RESULTS:** ILL AN and REC AN had significantly higher mean baseline TRP/LNAA (tryptophan/large neutral amino acids) ratios compared with CW. In contrast to placebo, the ATD challenge demonstrated a significantly greater reduction in the TRP/LNAA ratio for ILL AN (-95%) and REC AN (-84%) compared with CW (-70 %). Both the ILL AN and REC AN had a significant reduction in anxiety on the ATD day compared with the placebo day. **DISCUSSION:** These data demonstrate that a dietary-induced reduction of TRP, the precursor of serotonin, is associated with decreased anxiety in people with

AN. Restricting dietary intake may represent a mechanism through which individuals with AN modulate a dysphoric mood. Copyright 2003 by Wiley Periodicals, Inc.
Publication Types:

- Clinical Trial
- Randomized Controlled Trial

Domest Anim Endocrinol. 2003 Mar;24(2):137-53. National Center for Biotechnology Information at the U.S. National Library of Medicine. Thyrotropin-releasing hormone mediates serotonin-induced secretion of GH in cattle. Radcliff RP, Lookingland KJ, McMahon CD, Chapin LT, Tucker HA. Department of Animal Science, Michigan State University, East Lansing, MI 48824-1225, USA. radcliff@missouri.edu PMID: 12586314 [PubMed - indexed for MEDLINE]

Serotonin stimulates secretion of growth hormone (GH) in cattle, but the mechanism is unknown. In rats, thyrotropin-releasing hormone (TRH) mediates serotonin-induced secretion of GH. We hypothesized that the same is true in cattle. Cattle were fed for 2h daily to synchronize secretion of GH, such that concentrations of GH were high before and low after feeding. Our first objective was to determine whether or not feeding suppresses serotonin receptor agonist (quipazine) induced secretion of GH. Holstein steers were injected with quipazine (0.2 mg/kg BW) either 1 h before or 1 h after feeding. Quipazine-induced secretion of GH which did not differ in magnitude before and after feeding. If TRH mediates serotonin-induced secretion of GH, then magnitude of TRH-induced secretion of GH should not be different before and after feeding (our second objective). Sixteen meal-fed Holstein steers were injected with 0.3 microg TRH/kg BW either 1 h before or 1 h after feeding. Indeed, magnitude of TRH-induced secretion of GH before and after feeding was not different. Our third objective was to inhibit endogenous TRH with 3,5,3'-triiodothyronine (T(3)) and examine basal, GH-releasing hormone (GHRH)-, TRH- and quipazine-induced secretion of GH. Sixteen Holstein steers were injected daily with either T(3) (3 or 6 microg/kg BW) or vehicle for 20 days and then challenged sequentially with vehicle or GHRH, TRH, or quipazine. T(3) did not affect basal, GHRH- or TRH-induced secretion of GH, but reduced basal secretion of thyroxine. T(3) reduced but did not completely block quipazine-induced secretion of GH. In conclusion, TRH mediates, in part, serotonin-induced secretion of GH in cattle.

Nutr Neurosci. 2003 Feb;6(1):19-28. National Center for Biotechnology Information at the U.S. National Library of Medicine. Can the pathophysiology of autism be explained by the nature of the discovered urine peptides? Reichelt KL, Knivsberg AM. Institute of Pediatric Research, Univ of Oslo, Rikshospitalet, N0027, Oslo, Norway. k.l.reichelt@klinmed.uio.no PMID: 12608733 [PubMed -indexed for MEDLINE]

Opioid peptides derived from food proteins (exorphins) have been found in urine of autistic patients. Based on the work of several groups, we try to show that exorphins and serotonin uptake stimulating factors may explain many of the signs and symptoms seen in autistic disorders. The individual symptoms ought to be explainable by the properties and behavioural effects of the found peptides. The data presented form the basis of an autism model, where we suggest that exorphins and serotonin uptake modulators are key mediators for the development of autism. This may be due to a genetically based peptidase deficiency in at least two or more peptidases and, or of peptidase regulating proteins made manifest by a dietary overload of exorphin precursors such as by increased gut uptake.

Publication Types:

- Review
- Review, Tutorial

Neuropsychopharmacology. 2003 Jan;28(1):153-62. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues.** Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS. University Department of Psychiatry, University of Oxford, UK. robert.rogers@psych.ox.ac.uk PMID: 12496952 [PubMed -indexed for MEDLINE]

While accumulating evidence suggests that effective real-life decision-making depends upon the functioning of the orbitofrontal cortex, much less is known about the involvement of the monoamine neurotransmitter systems and, in particular, serotonin. In the present study, we explored the impact of depleting the serotonin precursor, tryptophan, on human decision-making. Eighteen healthy volunteers consumed an amino-acid drink containing tryptophan and 18 healthy volunteers consumed an amino-acid drink without tryptophan, before choosing between simultaneously presented gambles, differing in the magnitude of expected gains (ie reward), the magnitude of expected losses (ie punishment), and the probabilities with which these outcomes were delivered. Volunteers also chose between gambles probing identified non-normative biases in human decision-making, namely, risk-aversion when choosing between gains and risk-seeking when choosing between losses. Tryptophan-depleted volunteers showed reduced discrimination between magnitudes of expected gains associated with different choices. There was little evidence that tryptophan depletion was associated with altered discrimination between the magnitudes of expected losses, or altered discrimination between the relative probabilities with which these positive or negative outcomes were delivered. Risk-averse and risk-seeking biases were also unchanged. These results suggest that serotonin mediates decision-making in healthy volunteers by modulating the processing of reward cues, perhaps represented within the orbitofrontal cortex. It is possible that such a change in the cognition mediating human choice is one mechanism associated with the onset and maintenance of anhedonia and lowered mood in psychiatric illness.

Publication Types:

- . • Clinical Trial
- . • Randomized Controlled Trial

Neuropsychopharmacology. 2003 Jan;28(1):153-62. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues.** Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS. University Department of Psychiatry, University of Oxford, UK. robert.rogers@psych.ox.ac.uk PMID: 12496952 [PubMed - indexed for MEDLINE]

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unchanged. These results suggest that serotonin mediates decision-making in healthy volunteers by modulating the processing of reward cues, perhaps represented within the orbitofrontal cortex. It is possible that such a change in the cognition mediating human choice is one mechanism associated with the onset and maintenance of anhedonia and lowered mood in psychiatric illness.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

Int J Obes Relat Metab Disord. 2003 Jan;27(1):1-12. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Two forms of disordered eating in obesity: binge eating and night eating.** Stunkard AJ, Allison KC. Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA. stunkard@mail.med.upenn.edu PMID: 12532147 [PubMed - indexed for MEDLINE]

OBJECTIVE: Binge eating disorder (BED) and the night eating syndrome (NES) have been linked to obesity. This review summarizes their characteristics, implications of their diagnoses and treatment outcomes. METHOD: Selective review of the literature on BED and NES. RESULTS: BED was proposed as a distinctive disorder on the basis of two large multisite studies in the early 1990s. It is associated with more severe and earlier onset of obesity, earlier onset of dieting and greater psychopathology. It shows large placebo responses and reduction of bingeing in patients on waiting-list controls. Traditional weight reduction programs reduce bingeing at least as well as psychological treatments designed for this purpose. NES is a stress-related eating, sleeping and mood disorder that is associated with disordered neuroendocrine function. It follows a characteristic circadian pattern and has responded to an agent that enhances serotonin function. CONCLUSIONS: BED responds well to weight reduction programs. It is proposed that this diagnosis be used as a marker for psychological problems that deserve treatment in their own right. NES is an eating, sleep, and mood disorder with distinctive behavioral and neuroendocrine characteristics. Studies of treatment for NES are in their infancy but selective serotonin reuptake inhibitors (SSRI) show promise.

Publication Types:

- Review
- Review Literature

Int J Psychiatry Med. 2003;33(1):103-5. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Sertraline-induced hyperglycemia: case report.** Sansone RA, Sansone LA, Wright PMID: 12906348 [PubMed - indexed for MEDLINE] State University, Dayton, Ohio, USA. Randy.sansone@kmcnetwork.org

Empirical studies with humans suggest that selective serotonin reuptake inhibitors (SSRIs) may, through increases in serotonergic activity, increase insulin secretion, increase insulin sensitivity, and lower serum glucose levels. Indeed, the potentially beneficial effects of SSRI treatment in diabetics are documented. However, we describe the case of a female, with diet-controlled, type 2 diabetes, whose glucose levels increased with exposure to sertraline.

Publication Types:

- Case Reports Physiol Behav. 2003 Nov;80(2-3):243-52. National Center for Biotechnology Information at the U.S. National Library of Medicine. Effect of sibutramine on macronutrient selection in male and female rats. LeBlanc M, Thibault L. School of

Dietetics and Human Nutrition, McGill University-Macdonald Campus, 2111 Lakeshore Road, Ste-Anne-de-Bellevue, QC, Canada H9X 3V9. PMID: 14637222 [PubMed indexed for MEDLINE]

Sibutramine, a serotonin-noradrenaline reuptake inhibitor (SNRI), has been shown to be a safe and effective weight-loss drug. The purpose of the present study was to examine whether sibutramine has an effect on macronutrient selection in both female and male rats in addition to total food intake. Wistar rats of both sexes were divided into three groups, and each group was offered a different set of three sensorily contrasting macronutrient-specific diets, each set including carbohydrate-, protein-, and fat-rich diets. Sibutramine (10 mg/kg) was shown to consistently decrease carbohydrate and fat intake at all data points regardless of gender and diet. Intake of carbohydrate differed between male and female rats at 2 h post administration with 2.5 and 5 mg/kg of sibutramine. The effect of sibutramine on protein intake was diet- and gender-specific. All doses of sibutramine decreased total food intake regardless of gender and diet group beginning at 6 h post administration. In conclusion, sibutramine affected macronutrient selection and emphasis on dietary recommendations, as well as appropriate dosage according to gender should be considered during therapy.

Drugs Aging. 2003;20(2):85-100. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Effect of reproductive hormones and selective estrogen receptor modulators on mood during menopause.** Soares CN, Poitras JR, Prouty J. Harvard Medical School, MGH Center for Women's Mental Health, Boston, Massachusetts 02114, USA. csoares@partners.org PMID: 12534310 [PubMed - indexed for MEDLINE]

Periods of intense hormonal fluctuations have been associated with heightened prevalence and exacerbation of underlying psychiatric illness, particularly the occurrence of premenstrual dysphoria, puerperal depression and depressive symptoms during perimenopause. It has been speculated that sex steroids such as estrogens, progestogens, testosterone and dehydroepiandrosterone (DHEA) exert a significant modulation of brain functioning, possibly through interactions with various neurotransmitter systems. It is therefore intuitive that abrupt alterations of these hormones would interfere with mood and behaviour. On the other hand, accumulating data suggest that hormonal interventions may also promote relief or even remission of depressive symptoms, as already demonstrated in studies with patients experiencing postpartum depression and perimenopausal depressive disorders. The extent to which perimenopause, alone, may increase the risk for depression is unclear. However, existing data strongly suggest that some women are particularly vulnerable to developing significant physical and psychological disturbances when entering perimenopause. This article reviews the effect of sex hormones and selective estrogen receptor modulators (SERMs) on mood among peri- and postmenopausal women. There are preliminary, though promising, data on the use of estradiol (particularly transdermal estradiol) to alleviate depression during perimenopause, use of a combination of estrogens and selective serotonin reuptake inhibitors for depression during the postmenopausal period, and the use of testosterone to improve psychological well-being and increase libido among women with induced menopause. Further studies would help to better delineate the usage of hormones as an antidepressant strategy (monotherapy or augmenting treatment) for peri- and postmenopausal women. A brief review of some nonhormonal interventions for the treatment of menopause-related symptoms that may significantly affect a woman's quality of life is also presented. There are some preliminary data suggesting the efficacy of antidepressants for the treatment of hot flushes; existing data on diet supplements and herbal products have shown more mixed results.

Publication Types:

- . • Review
- . • Review, Tutorial

Am J Cardiovasc Drugs. 2002;2(4):245-53. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Pharmacotherapy of obesity: currently marketed and upcoming agents.** Bays H, Dujovne C. Louisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky, USA. PMID: 14727970 [PubMed - indexed for MEDLINE]

In many industrialized nations, obesity is now considered an epidemic, resulting in accelerated morbidity and mortality. Obesity is associated with an increased risk of coronary artery disease as well as the metabolic syndrome comprising abdominal obesity, increased fasting blood glucose levels, dyslipidemia and hypertension, which are all recognized cardiovascular risk factors. Diet, exercise, and lifestyle changes constitute important recommendations for treatment. Unfortunately, although effective in some individuals, these recommendations have proven to be ineffective in adequately addressing the broad, enlarging scope of this public health problem. Drug treatment is often indicated but is somewhat limited by the minimal number of well tolerated drugs that have proven to have long-term efficacy in maintaining bodyweight loss. For example, phentermine may result in modest bodyweight loss through suppression of appetite, but potential cardiovascular adverse effects exist and the efficacy is mainly short-term. Sibutramine, an inhibitor of serotonin and norepinephrine (noradrenaline) reuptake, may increase satiety and result in modest bodyweight loss. However, cardiovascular adverse effects may occur in susceptible patients. Nonetheless, sibutramine is one of the few drugs that has been approved by the US Food and Drug Administration (FDA) for bodyweight loss. Orlistat, a lipase inhibitor, is also approved by the FDA for bodyweight loss but may have bothersome gastrointestinal adverse effects, especially among patients who do not adhere to the recommended low-fat diet. Ongoing studies continue to evaluate other drug treatments that may result in bodyweight reduction through a number of different mechanisms. It is anticipated that the development of effective and well tolerated antiobesity drugs will elevate the pharmacologic treatment of obesity to the status of other cardiovascular risk factors and metabolic disorders. This may be especially important given that dyslipidemia, hypertension and type 2 diabetes mellitus are often secondary to, or exacerbated by, obesity.

Publication Types:

- . • Review
- . • Review, Tutorial
- .

Am J Clin Nutr. 2001 Nov;74(5):620-30. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Substrate oxidation and control of food intake in men after a fat-substitute meal compared with meals supplemented with an isoenergetic load of carbohydrate, long-chain triacylglycerols, or medium-chain triacylglycerols.** Van Wymelbeke V, Louis-Sylvestre J, Fantino M. Groupe Nutrition et Metabolisme Humain, Faculte de Medecine, Dijon, France. PMID: 11684530 [PubMed - indexed for MEDLINE]

BACKGROUND: It has been suggested that hunger may be delayed and food intake reduced under metabolic conditions that spare carbohydrate oxidation. **OBJECTIVE:** Our objective was to examine the role of glucose metabolism in the control of food intake in men by using medium-chain triacylglycerols (MCTs) to spare carbohydrate oxidation. **DESIGN:** In 10 male volunteers, isolated and deprived of any time cues, we studied the effects of 4 lunches on hunger ratings, the duration of satiety, the amount of food ingested at dinner, energy expenditure, substrate oxidation, and plasma variables until the time of the dinner request. One lunch was a basic 2310-kJ meal containing 40 kJ fat substitute (Sub lunch). The 3 other lunches consisted of the same basic meal supplemented with either 1200 kJ long-chain triacylglycerols (LCT lunch), 1200 kJ MCTs (MCT lunch), or 900 kJ carbohydrate plus 300 kJ LCTs (Cho lunch). **RESULTS:** Energy expenditure was not significantly different after the different lunches, but carbohydrate oxidation was lower

after the MCT and LCT lunches than after the Cho lunch. Fat oxidation was greater after the MCT and LCT lunches. The time of the dinner request was significantly delayed after the Cho lunch. Food intake at dinner was significantly lower after the MCT lunch than after the Sub and Cho lunches, but the dinner meal request was not delayed. **CONCLUSION:** Carbohydrate may have a greater role in the duration of satiety than does fat, but MCTs may play an active role in other aspects of the control of food intake, especially in satiation at the next meal.

Metabolism 2001 Apr;50(4):481-7 **Carbohydrate metabolism during exercise in females: effect of reduced fat availability.** Howlett KF, Spriet LL, Hargreaves M School of Health Sciences, Deakin University, Burwood, Australia.

This study examined the effect of reduced plasma free fatty acid (FFA) availability on carbohydrate metabolism during exercise. Six untrained women cycled for 60 minutes at approximately 58% of maximum oxygen uptake after ingestion of a placebo (CON) or nicotinic acid (NA), 30 minutes before exercise (7.4 0.5 mg.kg(-1) body weight), and at 0 minutes (3.7 0.3 mg.kg(-1)) and 30 minutes (3.7 0.3 mg.kg(-1)) of exercise. Glucose kinetics were measured using a primed, continuous infusion of [6,6-(2)H] glucose. Plasma FFA (CON, 0.86 0.12; NA, 0.21 0.11 mmol.L(-1) at 60 minutes, $P < .05$) and glycerol (CON, 0.34 0.05; NA, 0.10 0.04 mmol.L(-1) at 60 minutes, $P < .05$) were suppressed throughout exercise. Mean respiratory exchange ratio (RER) during exercise was higher ($P < .05$) in NA (0.89 0.02) than CON (0.83 0.02). Plasma glucose and glucose production were similar between trials. Total glucose uptake during exercise was greater ($P < .05$) in NA (1,876 161 micromol.kg(-1)) than in CON (1,525 107 micromol.kg(-1)). Total fat oxidation was reduced ($P < .05$) by approximately 32% during exercise in NA. Total carbohydrate oxidized was approximately 42% greater ($P < .05$) in NA (412 40 mmol) than CON (290 37 mmol), of which, approximately 16% (20 10 mmol) could be attributed to glucose. Plasma insulin and glucagon were similar between trials. Catecholamines were higher ($P < .05$) during exercise in NA. In summary, during prolonged moderate exercise in untrained women, reduced FFA availability results in a compensatory increase in carbohydrate oxidation, which appears to be due predominantly to an increase in glycogen utilization, although there was a small, but significant, increase in whole body glucose uptake.

Am J Clin Nutr 2000 Aug;72(2 Suppl):573S-8S **Serotonin and central nervous system fatigue: nutritional considerations.** Davis JM, Alderson NL, Welsh RS Department of Exercise Science, School of Public Health, University of South Carolina, Columbia, SC 29208, USA.

Fatigue from voluntary muscular effort is a complex phenomenon involving the central nervous system (CNS) and muscle. An understanding of the mechanisms within muscle that cause fatigue has led to the development of nutritional strategies to enhance performance. Until recently, little was known about CNS mechanisms of fatigue, even though the inability or unwillingness to generate and maintain central activation of muscle is the most likely explanation of fatigue for most people during normal daily activities. A possible role of nutrition in central fatigue is receiving more attention with the development of theories that provide a clue to its biological mechanisms. The focus is on the neurotransmitter serotonin [5-hydroxytryptamine (5-HT)] because of its role in depression, sensory perception, sleepiness, and mood. Nutritional strategies have been designed to alter the metabolism of brain 5-HT by affecting the availability of its amino acid precursor. Increases in brain 5-HT concentration and overall activity have been associated with increased physical and perhaps mental fatigue during endurance exercise. Carbohydrate (CHO) or branched-chain amino acid (BCAA) feedings may attenuate increases in 5-HT and improve performance. However, it is difficult to distinguish between the effects of CHO on the brain and those on the muscles themselves, and most studies involving BCAA show no performance benefits. It appears that important relations exist between brain 5-HT and central fatigue.

Physiol Behav 2000 Aug-Sep;70(3-4):333-42 **Effects of food on cortisol and mood in vulnerable subjects under controllable and uncontrollable stress.** Markus R, Panhuysen G, Tuiten A, Koppeschaar H TNO Nutrition and Food Research Institute, Utrechtseweg 48, P.O. Box 360, 3700 AJ, Zeist, The Netherlands.

The aim of this study was to investigate whether in stress-prone subjects, carbohydrate-rich, protein-poor food (CR/PP) diminished depressive mood and a cortisol response under controllable as well as uncontrollable laboratory stress. Twenty-two subjects with high stress proneness (HS) and 23 subjects with low stress proneness (LS) participated in a controllable- and uncontrollable-stress experiment during either a CR/PP or protein-rich, carbohydrate-poor (PR/CP) diet. Both controllable and uncontrollable laboratory stress significantly increased pulse rate and skin conductance in HS and LS subjects, whereas uncontrollable stress increased feelings of depression, anger, tension, and fatigue and decreased feelings of vigor. Only in HS subjects, a cortisol response and feelings of depression became lower under the CR/PP diet condition, irrespective of the controllability of the laboratory stressor, suggesting an increased ability to cope with stress. Because the CR/PP diet compared with the PR/CP diet previously has been found to cause a 42% increase in plasma tryptophan/SigmaLNAA, seen as an indirect measure of increases in brain serotonin levels, the present results suggest that an enhanced serotonin function in HS subjects may be involved.

Br J Nutr 1999 Dec;82(6):457-67 **Carbohydrate intake improves cognitive performance of stress-prone individuals under controllable laboratory stress.** Markus CR, Panhuysen G, Jonkman LM, Bachman M Department of Psychonomics, Utrecht University, The Netherlands.

Cognitive performance has been found to decline after exposure to stress, particularly in stress-prone subjects. The present study investigated whether a carbohydrate-rich, protein-poor (CR/PP) diet, which may enhance cerebral serotonin function in stress-prone subjects due to increases in the available tryptophan, improves the performance of stress-prone subjects after exposure to acute laboratory stress. Twenty-two high-stress-prone (HS) subjects and twenty-one low-stress-prone (LS) subjects aged between 19 and 26 years performed a memory scanning task after controllable and uncontrollable stress, following either a CR/PP diet or a protein-rich, carbohydrate-poor (PR/CP) isoenergetic diet. Uncontrollable stress reduced feelings of control ($F(1,38) 9.30$; $P = 0.004$), whereas pulse rate and skin conductance increased after both stress tasks ($F(1,38) 78.34$; $P = 0.0005$ and $F(1,37) 83.16$; $P = 0.0004$). Diet, stress-proneness and stress-controllability interacted ($F(1,36) 9.46$; $P = 0.004$) in such a way that performance in HS subjects was better with the CR/PP diet than with the PR/CP diet, but only after controllable stress. As the CR/PP diet has been found to increase the plasma tryptophan: large neutral amino acids ratio, indicating an increased availability of cerebral tryptophan and, thus, higher serotonin levels, it appears that there may be an increased availability of brain serotonin in HS subjects after controllable laboratory stress.

Eur J Clin Nutr. 1999 Apr;53 Suppl 1:S148-65. **National Center for Biotechnology Information at the U.S. National Library of Medicine. High and low carbohydrate and fat intakes: limits imposed by appetite and palatability and their implications for energy balance.** Blundell JE, Stubbs RJ. Psychology Department, University of Leeds, UK. PMID: 10365993 [PubMed - indexed for MEDLINE]

This report examines several issues concerning the effects of dietary fats and carbohydrates (CHOs) on body weight and the limits set on the intake of these nutrients by factors influencing appetite control: (i) the physiological relationship between feeding behaviour (FB) and body

weight; (ii) the distribution of nutrients in Western foods and the implications this may have for FB; (iii) the contribution of nutrients in the diet, to total EI under both extreme and typical Western conditions; (iv) the known effects that fats, CHOs and dietary energy density (ED) exert on appetite and energy balance (EB); (v) the potential role of sensory factors in promoting or limiting fat, CHO and energy intakes (EI) in modern human populations. Population studies and large surveys have identified individuals with wide ranges of fat and CHO intakes. Intakes of fat can vary from an average of 180 g/day to 25 g/day in a representative sample. But on individual days fat intake can rise to well over 200 g according to a selection of high fat foods. In a single meal, people can consume an amount of fat greater than the population daily average. From this analysis it can be deduced that the appetite control mechanism will permit the consumption of large amounts of fat (if an abundance of high fat foods exist in the food supply). Except for specific physiological circumstances (e.g. endurance explorers) where there is an urgent need for EIs, in the face of decreasing body weight, it is unlikely that the body will generate a specific drive for fat. Because CHO foods have a lower ED than fat foods (on average) and because of their greater satiating capacity, the free intake of high CHO foods is likely to be self-limiting (at lower EIs than those generated by fatty foods). This does not mean that excess EIs are impossible when people feed ad libitum on high CHO diets.

Publication Types:

- Review
- Review, Academic

Am J Physiol 1998 Oct;275(4 Pt 2):R1164-73 **Differential catecholamine responses to protein intake in healthy and hypertensive subjects.** Kuchel O Clinical Research Institute of Montreal and Hotel-Dieu Hospital, University of Montreal, Montreal, Quebec, Canada H2W 1R7.

Protein intake-induced natriuresis previously related to increased urinary dopamine excretion was reexamined in an extensive controlled study comparing healthy and hypertensive subjects. In healthy subjects, ingestion of 1 g/kg wt tuna induced natriuresis that was associated, between postprandial hours one and two, with increased plasma tyrosine [191 13% (mean SE); $P < 0.01$], 3, 4-dihydroxyphenylalanine (104 12%, $P < 0.05$ in plasma; 162 20%, $P < 0.05$ in urine), plasma free dopamine (156 32%; $P < 0.05$), and dopamine sulfate (191 11%, $P < 0.001$ in plasma; 199 15%, $P < 0.01$ in urine) but affected urinary free dopamine excretion only at limits of significance. Hypertensive subjects had less ($P < 0.02$) natriuresis and, despite comparable plasma tyrosine and dopamine sulfate increases, no increase in plasma and urinary 3, 4-dihydroxyphenylalanine and plasma free dopamine. Their plasma and urinary free epinephrine responses were less ($P < 0.05$) than the borderline increases in control subjects. Compared with control subjects, they significantly increased plasma 3, 4-dihydroxyphenylalanine sulfate ($P < 0.05$), epinephrine sulfate ($P < 0.05$), and the dopamine sulfate-to-free dopamine ratio ($P < 0.02$). Postprotein natriuresis is thus associated with nutritional priming-induced plasma but not urinary free dopamine increase. Hypertensive subjects have attenuated natriuretic and plasma free dopamine responses and less free epinephrine increase. This may partly result from higher circulating 3, 4-dihydroxyphenylalanine, dopamine, and epinephrine sulfoconjugates leaving fewer free amines for biological actions.

Markus CR, Panhuysen G, Tuiten A, Koppeschaar H, Fekkes D, Peters ML **“Does carbohydrate-rich, protein-poor food prevent a deterioration of mood and cognitive performance of stress-prone subjects when subjected to a stressful task?”** *Appetite* 1998 Aug; 31(1): 49-65 Department of Psychonomics, Utrecht University, The Netherlands.

This study investigates whether in stress-prone subjects, carbohydrate-rich, protein-poor food (CR/PP) prevents a deterioration of mood and performance under uncontrollable laboratory stress conditions. The assumption was that in stress-prone subjects there is a higher risk of serotonin deficiency in the brain and that carbohydrates may prevent a functional shortage of central serotonin during acute stress, due to their potentiating effect on brain tryptophan. Twenty-four subjects with a high stress-proneness (HS) and 24 subjects with a low stress-proneness (LS) participated in an uncontrollable stress situation under both a CR/PP and a protein-rich, carbohydrate-poor (PR/CP) diet condition. The plasma ratio of tryptophan to the other large neutral amino acids (LNAA) (ratio tryptophan/summation operator LNAA) was determined as a measure indicating the dietary effect on brain tryptophan and serotonin levels. Significant increases were found in the ratio tryptophan/summation operator LNAA during the CR/PP diet compared with the PR/CP diet. Experimental stress had significant effects on pulse rate, skin conductance, cortisol and mood in all subjects. During the CR/PP diet only the HS subjects did not show the stress-induced rise in depression, decline in vigour and cortisol elevation that they showed after the PR/CP diet. With respect to cognitive performance, significant dietary effects were found on reaction time. It is suggested that CR/PP food in HS subjects may increase personal control, probably under the influence of higher levels of brain tryptophan and serotonin.

Brain Res Bull 1997;43(1):43-6 **Changes in the albumin binding of tryptophan during postoperative recovery: a possible link with central fatigue?** Yamamoto T, Castell LM, Botella J, Powell H, Hall GM, Young A, Newsholme EA University Department of Biochemistry, Oxford, UK.

Tryptophan is the precursor of the neurotransmitter 5-hydroxytryptamine (5-HT), known to be involved in sleep and fatigue. In the blood, tryptophan binds to albumin, and that which does not, free tryptophan, competes with branched chain amino acids (BCAA) for entry into the brain. The plasma concentrations of albumin, free tryptophan, total tryptophan, and BCAA were measured before and after major surgery in nine elderly and nine coronary artery bypass graft (CABG) patients. In both the elderly and the CABG patients plasma free tryptophan concentrations were increased after surgery, compared with baseline levels; the plasma free tryptophan/BCAA concentration ratio was also increased significantly after surgery. Plasma albumin concentrations were decreased significantly after surgery in both the elderly and the CABG patients. Plasma BCAA concentrations were not affected by surgery in either group. The effect of exercising to exhaustion on 5-HT and tryptophan were investigated in Nagase albuminemic rats (NAR). The intrasynaptosomal concentration of tryptophan, 5-hydroxy-tryptophan, and 5-HT was increased by fatigue after exercise. In addition, running time to exhaustion was shortened in NAR. These data suggest that free tryptophan uptake and 5-HT synthesis were enhanced in the nerve terminal. A decrease in plasma albumin may account for the increase in plasma-free tryptophan levels. An increase in plasma free tryptophan, resulting in an enhanced plasma concentration ratio of free tryptophan/BCAA, may lead to a higher 5-HT concentration in some parts of the brain and, consequently, to central fatigue. It is suggested that provision of BCAA as a dietary supplement may counteract the increase in plasma free tryptophan and thus improve the status of some patients after major surgery.

Neumeister A, Praschak-Rieder N, Hesselmann B, Tauscher J, Kasper S “The tryptophan depletion test. Basic principles and clinical relevance” Nervenarzt 1997 Jul; 68(7): 556-62

The application of a tryptophan-free amino acid mixture (tryptophan depletion test) induces a rapid and substantial lowering of both total and free plasma tryptophan. Consequently, the brain serotonin content and also cerebral serotonin function are decreased. This method provides a paradigm to study the role of serotonin in the pathobiology of depressive disorders and their treatment modalities. Untreated depressed patients show few behavioral effects during tryptophan depletion. In depressed patients during an antidepressant or light-therapy-induced stable remission, a transient depressive relapse was induced by tryptophan depletion. Healthy subjects with a genetic risk for affective disorder show worsening of their condition induced by tryptophan depletion. These findings indicate the relevance of altered brain serotonin function in the pathophysiology of affective disorders and strengthen the importance of serotonin in the mechanism of action of antidepressants. Since recently published studies revealed some evidence that the serotonergic system is directly involved in the pathophysiology of various psychiatric syndromes besides depression, it seems to be reasonable to evaluate the validity of the tryptophan depletion test also in non-depressed patients.

Int J Obes Relat Metab Disord. 1997 Jun;21 Suppl 3:S2-11. National Center for Biotechnology Information at the U.S. National Library of Medicine. **The role of dietary fat in obesity.** Golay A, Bobbioni E. Teaching Diabetic Division, Geneva University Hospital, Switzerland. EPIDEMIOLOGY: Epidemiological evidence suggests that a high-fat PMID: 9225171 [PubMed - indexed for MEDLINE

EPIDEMIOLOGY: Epidemiological evidence suggests that a high-fat diet promotes the development of obesity and that there is a direct relationship between the amount of dietary fat and the degree of obesity. The importance of this relationship has been shown in black prepubescent females, who consumed more calories as fat than white females. Moreover, black adult females are heavier and have significant higher cardiovascular disease mortality rates than white females. **THE INFLUENCE OF DIETARY FAT ON FOOD INTAKE:** An overview of animal studies had indicated that high-fat diets induce greater food intake and weight gain than high-carbohydrate diets. Several factors such as caloric density, satiety properties and postabsorptive processing can contribute to this different response to high-fat diets. Accordingly, the satiating effects after meals with a high fat:carbohydrate ratio is less than for meals with a lower ratio. Some authors have reported that the most important variable influencing meal size is not the level of hunger but the nutrient content of the range of foods consumed. Thus dietary fat has a weak effect on satiety and we suggest that periodic exposure to a high-fat meal, particularly when hunger is high, may be sufficient to lead to overconsumption of energy as fat in obese patients. **DIETARY FAT AND FAT BALANCE:** Energy balance is well correlated with fat balance in lean controls, whereas there is no correlation with either carbohydrate or protein balances. Several authors have shown that carbohydrate and protein storage is closely regulated by adjusting oxidation to intake, whereas fat is almost exclusively used or stored in response to day-to-day fluctuations in energy balance. The positive relationship between fat intake and lipid oxidation seen in lean controls appears not to be present in obese patients. On high-fat diets, post-obese women failed to increase the ratio of fat to carbohydrate oxidation appropriately. Increasing dietary fat results in preferential fat storage in post-obese women, impaired suppression of carbohydrate and reduction of 24h energy expenditure. **CONCLUSIONS:** Dietary fat induces overconsumption and weight gain through its low satiety properties and high caloric density. Obese and post-obese subjects do not appear to adapt to dietary fat, and therefore fat storage is increased.

Publication Types:

- . • Review
- . • Review, Tutorial

Life Sci 1996 May 24; 58(26): 2389-95 **“Decrease in plasma phenylalanine and tyrosine after phenylalanine-tyrosine free amino acid solutions in man.”** Moja EA, Lucini V, Benedetti F, Lucca A Chair of Medical Psychology, University of Milan, Padiglione L.I.T.A., Ospedale L. Sacco.

After an overnight fast, five male healthy subjects ingested increasing amounts of a solution containing a fixed proportion of seven essential amino acids (L-isoleucine, 13.3%; L-leucine, 21.0%; L-lysine, 15.2%; L-methionine, 21.0%; L-threonine, 9.5%; L-tryptophan, 4.8% and L-valine, 15.2%) and lacking phenylalanine and tyrosine. The solutions caused a rapid fall in plasma phenylalanine and tyrosine which was proportional to the total amount of amino acids ingested. Following the highest dose administered (31.5 g) plasma phenylalanine and tyrosine fell to a minimum of, respectively, 12.7% and 29.8% the initial levels and remained markedly reduced at six hours after treatment.

Obes Res. 1995 Jul;3(4):345-56. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Serotonergic manipulation, meal-induced satiety and eating pattern: effect of fluoxetine in obese female subjects.** Lawton CL, Wales JK, Hill AJ, Blundell JE. Department of Psychology, School of Medicine, University of Leeds, UK. PMID: 8521151 [PubMed - indexed for MEDLINE]

Twelve nondepressed healthy female obese subjects (BMI > 30 kg/m²) took part in a study which conformed to a double-blind randomized crossover design. Each subject acted as her own control across 2 weeks of treatment with either 60 mg of the 5-HT reuptake inhibitor fluoxetine or matching placebo. On days 7 and 14 of both treatment phases subjects were provided with fixed energy lunch meals high in either CHO or fat. The effect of these meals on satiety during the fluoxetine and placebo phases was assessed by a battery of procedures. Subjects felt less hungry after consuming the high CHO meal than after consuming the high-fat meal. They also felt less hungry when taking fluoxetine than when taking the placebo. Analysis of energy intake from the test meal revealed a main effect of prior lunch meal type (high CHO or high fat) and a main effect of drug treatment. Subjects consumed an average of 574 kcal following the high CHO meal compared to 689 kcal following the high-fat meal. Subjects also consumed an average of 532 kcal when taking fluoxetine compared to 730 kcal when taking the placebo. Fluoxetine did not exert any significant effects on macronutrient selection. Mean daily energy intake, calculated from food diary records, was 1881 kcal when subjects were taking the placebo compared to 1460 kcal when taking fluoxetine (a reduction of 22.4%). Fluoxetine treatment produced a significant weight loss of 1.97 kg over the two weeks of treatment compared to a weight loss of only 0.04 kg on placebo.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

Young SN **“The use of diet and dietary components in the study of factors controlling affect in humans: a review.”** J Psychiatry Neurosci 1993 Nov;18(5):235-44

Although one of the first biological treatments of a major psychiatric disorder was the dietary treatment of pellagra, the use of diet and dietary components in the study of psychopathology has not aroused much interest. This article reviews three areas in which the dietary approach has provided interesting information. The tryptophan depletion strategy uses a mixture of amino acids devoid of tryptophan to lower brain tryptophan in order to study the symptoms that can be elicited. One effect of tryptophan depletion is a lowering of mood, the magnitude of

which seems to depend on the baseline state of the subject. Therefore, recovered depressed patients often undergo an acute relapse, while normal subjects show more moderate changes of mood. Totally euthymic subjects show no lowering of mood, but subjects with high normal depression scale scores or subjects with a family history of depression show a moderate lowering of mood. These data indicate that low serotonin levels alone cannot cause depression. However, serotonin does have a direct effect on mood, and low levels of serotonin contribute to the etiology of depression in some depressed patients. Folic acid deficiency causes a lowering of brain serotonin in rats, and of cerebrospinal fluid 5-hydroxyindoleacetic acid in humans. There is a high incidence of folate deficiency in depression, and there are indications in the literature that some depressed patients who are folate deficient respond to folate administration. Folate deficiency is known to lower levels of S-adenosylmethionine, and S-adenosylmethionine is an antidepressant that raises brain serotonin levels. These data suggest that low levels of serotonin in some depressed patients may be a secondary consequence of low levels of S-adenosylmethionine. They also suggest that the dietary intake and psychopharmacological action of methionine, the precursor of S-adenosylmethionine, should be studied in patients with depression. Normal meals have definite effects on mood and performance in humans. The composition of the meal, in terms of protein and carbohydrate content, can influence these behaviors.

Mullen BJ, Martin RJ **“The effect of dietary fat on diet selection may involve central serotonin.”** In: Am J Physiol (1992 Sep) 263(3 Pt 2):R559-63

Rats consuming a diet of 34% tallow select more protein and less carbohydrate than rats fed either 5% corn oil or tallow or 34% corn oil (25). To examine potential mechanism(s) of this phenomenon, we fed rats diets containing either tallow or corn oil at levels of 5 or 34% for two days. Sera were analyzed, and rats fed 34% tallow had higher serum insulin compared with those fed 34% corn oil. In a second experiment, rats were fed either 34% corn oil or tallow for two days. Brain tissues were analyzed, and rats fed 34% tallow had elevated serotonin in the raphe area compared with those fed 34% corn oil. In a third experiment, rats were fed either 34% corn oil or tallow for two days and then given dl-fenfluramine before diet selection. Fenfluramine depressed food intake to a greater degree in rats fed 34% tallow compared with those fed corn oil. These findings suggest that the diet selection behavior observed in tallow-fed rats may be mediated by a central serotonin system.

Venero JL, Herrera AJ, Machado A, Cano J **“Changes in neurotransmitter levels associated with the deficiency of some essential amino acids in the diet.”** Br J Nutr (1992 Sep) 68(2): 409-20

The contents of dopamine (DA) and serotonin (5-HT) and their metabolites were measured in rat substantia nigra and corpus striatum following dietary changes, including restriction of protein content (low-protein diet; LPD) and the contents of several large neutral amino acids (isoleucine, leucine, methionine, phenylalanine, tryptophan and valine) for 25 d. The LPD produced an increase in the concentration of tyrosine (TYR) in the two regions of the brain studied. This effect was also observed with all amino acid deficiencies studied except for valine in the substantia nigra, tryptophan in the striatum and phenylalanine in both regions. Likewise, the concentration of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of 5-HT, increased in the substantia nigra but not in the striatum after LPD, as well as with all the amino acid deficiencies studied, with the exception of tryptophan deficiency. In this case there was a dramatic effect on all components of the serotonergic system, with decreases in the concentration of tryptophan (TRP; precursor), 5-HT and 5-HIAA. This behaviour clearly shows an interrelationship between precursor (TRP) availability and 5-HT synthesis and metabolism. With valine deficiency, dopaminergic and serotonergic systems demonstrated opposite effects in the substantia nigra and the corpus striatum, and the behaviour of the two monoamines was also opposite within each structure.

Kema IP, Schellings AM, Meiborg G, Hoppenbrouwers CJ, Muskiet FA **“Influence of a serotonin- and dopamine-rich diet on platelet serotonin content and urinary excretion of biogenic amines and their metabolites.”** Clin Chem (1992 Sep) 38(9):1730-6

Using high-performance liquid chromatography and gas chromatography, we reevaluated the 24-h influence of a serotonin- and dopamine-rich diet on platelet serotonin and serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and major catecholamine metabolites in the urine of 15 healthy adults. Although there were significant responses in urinary free serotonin and catecholamine metabolites, their concentrations did not exceed the upper limits of the reference ranges for any of the participants. For urinary 5-HIAA, pronounced effects were observed within 2-4 h. After 6-8 h, results for 11 participants exceeded the upper limit of the reference range. The median recovery of dietary serotonin as urinary 5-HIAA was 20% and subject to a large range (150%). There was no significant change in platelet serotonin. We conclude that, using specific analytical methods, no dietary restrictions need be imposed to diagnose catecholamine (metabolite)-producing tumors. For diagnosis of carcinoids on the basis of urinary 5-HIAA it is appropriate to completely abstain from serotonin-containing foods for greater than or equal to 12 h before testing. Platelet serotonin is a more sensitive marker for carcinoids that produce only small amounts of serotonin, and is unaffected by dietary serotonin.

Blum I, Vered Y, Graff E, Grosskopf Y, Don R, Harsat A, Raz O **“The influence of meal composition on plasma serotonin and norepinephrine concentrations.”** Metabolism (1992 Feb) 41(2):137-40

Reports concerning changes in plasma neurotransmitter values that result from dietary manipulations have not been published so far. The influence of various meal compositions on platelet-poor plasma (PPP) serotonin (5-HT) and norepinephrine (NE) levels was investigated. Healthy volunteers were subjected to three test meals: a carbohydrate-rich meal (86% carbohydrates), a protein-rich meal (70% protein), and a fat-rich meal (92% fat). After a carbohydrate-rich meal, PPP 5-HT values increased significantly (4.47-fold, P less than .02), whereas a smaller increase (1.66-fold, P = NS) was observed after a fat-rich meal. These effects on PPP 5-HT values could be correlated with insulin plasma levels. A protein-rich meal significantly reduced (P = 0.0011) PPP 5-HT to 28% of initial values, despite an increase in plasma insulin levels. This study has shown that (1) changes in meal compositions influence PPP 5-HT and, to a lesser extent, NE values; (2) the resulting changes in PPP 5-HT levels parallel those reported for brain neurotransmitters; and (3) these results seem to indicate that PPP 5-HT levels may be a model for brain synthesis and release of 5-HT.

Int J Obes. 1990 Mar;14(3):219-33. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Sensitivity of the appetite control system in obese subjects to nutritional and serotonergic challenges.** Hill AJ, Blundell JE. Psychology Department, University of Leeds, UK. PMID: 2187822 [PubMed -indexed for MEDLINE]

The sensitivity of the appetite system of a group of obese individuals was assessed in response to two challenges known to reduce hunger and enhance satiety in lean people. The challenges were the presentation of a caloric (high protein) load and the activation of serotonin systems. Eight obese female adults (BMI = 38) received 2 X 15 mg d-fenfluramine or placebo daily for 3 days, the study conforming to a 2 X 2 factor (drug X lunch type), double blind, repeated measures design. Three hours after dosing on day 3 they ate either a high carbohydrate (63 percent of total energy) or high protein (54 percent) lunchtime meal (the caloric load). These fixed meal challenges were equal in energy (475 kcal), weight and fat content. Ratings of hunger motivation and food preferences were tracked over the course of lunch and for a further 3 hours, at which

point subjects returned for a self-selection test meal. Intakes from this second open meal revealed significant main effects of both caloric load and drug on energy intake, with the high protein dfenfluramine combination being the most potent anorectic pairing. These findings were supported by the profiles of hunger motivation. This study has confirmed that the appetite system of these subjects was responsive to these biologically relevant challenges. The results suggest that the combination of an appetite modulating drug with specific dietary intervention may represent an effective strategy for the management of hunger arising from caloric restriction.

Publication Types:

- Clinical Trial
- Controlled Clinical Trial

Young SN, Pihl RO, Ervin FR **“The effect of altered tryptophan levels on mood and behavior in normal human males.”** Clin Neuropharmacol 1988;11 Suppl 1:S207-15 Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

The effect of lowering or raising tryptophan levels was studied in normal males using amino acid mixtures that were tryptophan free or tryptophan supplemented. Tryptophan depletion caused a small but significant alteration in food selection in subjects allowed to select from a buffet. Although carbohydrate and total kilocalories selected were unchanged, significantly less protein was chosen. Tryptophan depletion also caused an acute lowering of mood, suggesting that low serotonin (5-HT) may be involved in the etiology of clinical depression in some patients. No effect of altered tryptophan levels was seen in a laboratory test of aggression. However, a study on vervet monkeys indicated that altered tryptophan levels can influence aggression when the animals are at a high level of arousal. High arousal is known to increase the firing rate of 5-HT neurons. In a preliminary study, tryptophan had a therapeutic effect in aggressive schizophrenic patients. The best effect was seen in impulsive patients, which may have been related to high arousal in these subjects. Although carbohydrate is capable of raising brain tryptophan, not all carbohydrate-induced behaviors are mediated by tryptophan. Thus, sucrose was capable of attenuating alcohol intoxication in normal human males without altering blood alcohol concentrations. However, tryptophan had no effect on ethanol intoxication. The challenge for the future is to define the conditions under which alterations in tryptophan levels can influence brain function.

Decreases of brain serotonin following a food restriction schedule of four weeks in male and female rats. Haider S, Haleem DJ Med Sci Monit, 6(6): 1061-70

Male and female rats fed on a restricted feeding (RF) schedule of four weeks to produce 20-25% reduction in body weight, were killed before (starved) and after (fed) the presentation of food to compare 5-hydroxytryptamine (5-HT) metabolism in the hypothalamus with respective freely feeding (FF) controls and to monitor sex differences in RF-induced changes of 5-HT. RF decreased plasma tryptophan concentration in RF starved and RF fed females and also in RF starved males. In the hypothalamus tryptophan levels decreased in RF starved and RF fed female rats and RF fed males. 5-HT decreased in both RF starved and RF fed male and female rats and the decreases were comparable in the two sexes. 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of 5-HT was not affected. Food restriction decreased 5-HT concentration in the rest of the brain of male but not female rats. Possible implications of the findings in the pathogenesis of food restriction/starvation related disease anorexia nervosa and its greater occurrence in women than men is discussed.

Choi SW, Lee WJ, Choi Y. Department of Food Science and Nutrition, Catholic University of Daegu, 330 Keumrak 1 ri, Hayang-up, Gyeongsan-si, Gyeongbuk 712-702, Korea. shcho@cu.ac.kr PMID: 15228215 [PubMed - in process]

Six polyphenolic compounds were isolated from ethylacetate extract secondary to 80% ethanol extraction of defatted safflower seeds. They were categorized into three types: lignans, flavones and serotonin derivatives. Female Sprague-Dawley rats weighing 163.4 +/- 6.3 g were ovariectomized (Ovx) and fed either ethylacetate extract at a level of 1% (w/w) or three types of safflower polyphenolic compounds at a level of 200 mg/kg in a diet containing 0.5% (w/w) cholesterol for four wk. The sham and Ovx control groups were fed the same diet without safflower components. Plasma GOT and GPT levels did not differ among the six experimental groups. The plasma levels of total cholesterol were reduced in the four safflower groups by 2030% as compared to the Ovx control. The plasma level of HDL-cholesterol was higher in the Ovx+ethylacetate extract group or appeared to be in the three Ovx+safflower polyphenolic groups than in the Ovx control. The level of plasma triglyceride was also significantly lower in the Ovx+lignan group than in the Ovx control. The liver level of cholesterol was significantly reduced in the Ovx+ethylacetate extract group. Fecal excretion of cholesterol increased by the safflower lignans and flavones, whereas that of bile acid was not significantly changed by the safflower polyphenols. Matairesinol and acacetin isolated from safflower seeds reduced the cholesterol content in cultured HepG2 cells at a concentration of 0.01-0.1 microM and all three safflower polyphenolics decreased triglyceride content at the concentration of 0.1 microM. These results suggest that safflower polyphenols have the effect of improving blood lipid status via increasing HDL-cholesterol formation and cholesterol excretion without significant uterotrophic action in estrogen-deficient animals.

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Behavioral and other Assumptions:

Brain Res Mol Brain Res. 2004 Aug 23;127(1-2):39-47. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Differential expression of 5-HT(2A) and 5-HT(2C) receptor mRNAs in mice prone, or resistant, to chronic high-fat diet-induced obesity.** Huang XF, Han M, Storlien LH. Molecular Neurobiology Laboratory, Department of Biomedical Science, University of Wollongong, Wollongong, NSW 2522, Australia. PMID: 15306119 [PubMed -in process]

The present study examined the levels of 5-HT(2A) and 5-HT(2C) (2A and 2C receptors of 5hydroxytryptamine; serotonin) receptor messenger RNA (mRNA) expressions in the brain of chronic high-fat diet-induced obese (DIO) and obese-resistant (DR) mice. Thirty-one mice were used in this study. Twenty-four mice were fed with a high-fat diet (HF: 40% of calories from fat) for 4 weeks and then classified as the DIO (n=8) or DR (n=8) mice according to the highest and lowest body weight (BW) gainers. Seven mice were placed on a low-fat diet (LF: 10% of calories from fat) and were used as controls. After 20 weeks of feeding, the visceral fat accumulation was 620+/-42 mg in the DIO group versus 198+/-89 mg in the DR and 84+/-18 mg in the LF groups. Using quantitative in situ hybridization techniques, levels of 2A and 2C serotonin (5-HT) receptor mRNAs were measured in multiple brain sections of mice from the three groups. Most regions did not differ between groups but, importantly, the DIO mice had a significantly higher level of 5-HT(2A) receptor mRNA expression in the olfactory nucleus (Olf) compared to the DR and LF mice (+30% and +37%, respectively). The levels of Olf 5-HT(2A) receptor mRNA expression were related to body fat mass. The level of 5-HT(2C) mRNA receptor expression in the ventromedial hypothalamic (VMH) nucleus was 40% higher in the DIO mice than in the LF mice. Furthermore, the 5-HT(2C) receptor mRNA expression in the posterodorsal part of the medial amygdaloid (MePD) nucleus was 25% higher in the DIO mice than in the DR mice. The level of VMH 5-HT(2C) receptor mRNA expression was correlated with body fat mass. In conclusion, this

study has demonstrated differentially regulated levels of the 5-HT(2A) and 5-HT(2C) receptor mRNA expressions in the specific brain regions of the DIO and DR mice. It provides neural anatomical bases that the 5

Psychiatr Pol. 2004 Mar-Apr;38(2):227-39. National Center for Biotechnology Information at the U.S. National Library of Medicine. **Escitalopram--second generation of serotonin transporter inhibitors?** Rybakowski J, Borkowska AB. Z Kliniki Psychiatrii Doroslych AM w Poznaniu. PMID: 15307289 [PubMed - in process]

Escitalopram is the first antidepressant introduced according to chirality rules, it is an S-enantiomer of citalopram, the drug which has been used for many years. Experimental studies showed that the property of serotonin transporter inhibition--one of the main mechanisms of antidepressive action is connected with the S-enantiomer of citalopram, and that escitalopram is the most selective inhibitor of this transporter. The results of most clinical studies in patients with depression show significant superiority of escitalopram, 10-20 mg/day, over placebo, as early as within the first week of treatment, and a faster onset of action and higher therapeutic efficacy of escitalopram, compared to citalopram, 20-40 mg/day. A similar efficacy of escitalopram, 10 mg/day, and sertraline 50-200 mg/day, as well as escitalopram, 20 mg/day, and venlafaxine, 225 mg/day was demonstrated. It has also been shown that escitalopram, 10-20 mg/day, exerts therapeutic efficacy in general anxiety disorder, panic disorder and social phobia. Escitalopram may meet many criteria for the optimal antidepressant. The drug is efficacious in depressions of various intensity, has a rapid onset of action and, in long-term treatment, prevents the relapses of the illness. It exerts therapeutic activity in anxiety disorders. The dosing is convenient, and the drug is safe and well tolerated due to a mild profile of side-effects and favorable pharmacokinetic properties. Further studies are needed, aiming e.g. at the comparison of the therapeutic efficacy of escitalopram with other antidepressant drugs in different patients and the assessment of the effect of the drug on cognitive functions. The results of such studies may provide a convincing answer to the question whether escitalopram can be regarded as an antidepressant drug belonging to the second generation of serotonin transporter inhibitors.

Prog Cardiovasc Nurs 2001 Winter;16(1):5-13 **The effects of music on cardiac patients on bed rest.** Cadigan ME, Caruso NA, Haldeman SM, McNamara ME, Noyes DA, Spadafora MA, Carroll DL Department of Nursing, Patient Care Services, Massachusetts General Hospital, Boston, MA 02114, USA.

Hospitalizations that require invasive cardiac procedures or support with an intra-aortic balloon pump can be unsettling. This study was undertaken to measure the effect of a music intervention on physiologic and psychological responses of patients on bed rest due to procedural sheaths or an intra-aortic balloon pump. A randomized, two-group, pretest/post-test design was utilized to measure the effect of a 30-minute music intervention on heart rate, blood pressure, respiratory rate, skin temperature, pain perception, and mood states. One hundred forty subjects participated, 65 in the control group and 75 in the treatment group. There were no significant differences between the groups in demographic, clinical, or baseline variables, except for respiratory rate. After the music intervention, there were reductions in blood pressure, respiratory rate, and psychological distress, as measured by the Profile of Mood States ($p < 0.05$). Music appeared to affect selected physiologic responses and reduce psychological distress in patients on bed rest.

Indian J Physiol Pharmacol 2001 Jan;45(1):37-53 **Effect of yogic exercises on physical and mental health of young fellowship course trainees.** Ray US, Mukhopadhyaya S, Purkayastha SS, Asnani V, Tomer OS, Prashad R, Thakur L, Selvamurthy W Defence Institute of Physiology and Allied Sciences, Lucknow Road, Delhi-110 054.

A study was undertaken to observe any beneficial effect of yogic practices during training period on the young trainees. Fifty-four trainees of 20-25 years age group were divided randomly in two groups, i.e. yoga and control group. Yoga group (23 males and five females) was administered yogic practices for the first five months of the course while control group (21 males and five females) did not perform yogic exercises during this period. From the 6th to 10th month of training both the groups performed the yogic practices. Physiological parameters like heart rate, blood pressure, oral temperature, skin temperature in resting condition, responses to maximal and submaximal exercise, body flexibility were recorded. Psychological parameters like personality, learning, arithmetic and psychomotor ability, mental well-being were also recorded. Various parameters were taken before and during the 5th and 10th month of training period. Initially there was relatively higher sympathetic activity in both the groups due to the new work/training environment but gradually it subsided. Later on at the 5th and 10th month, yoga group had relatively lower sympathetic activity than the control group. There was improvement in performance at submaximal level of exercise and in anaerobic threshold in the yoga group. Shoulder, hip, trunk and neck flexibility improved in the yoga group. There was improvement in various psychological parameters like reduction in anxiety and depression and a better mental function after yogic practices.

Aust Fam Physician 2001 Jan;30(1):25-8 **How humour keeps you well.** Hassed C Department of Community Medicine and General Practice, Monash University, Victoria.

BACKGROUND: The beneficial effect of humour on health has long been recognized anecdotally and intuitively but studying and quantifying that effect is difficult. 'Studying humour is like dissecting a frog--you may know a lot but you end up with a dead frog.' (Mark Twain)
OBJECTIVE: To describe some of the psychological and physiological effects of laughter and the health benefits of humour. **DISCUSSION:** Stress reduction has been shown to improve outcomes in the treatment of many health problems. While there are inherent difficulties in structuring studies to assess the impact of humour and laughter on health, positive psychological and physiological responses to laughter have been demonstrated in a variety of settings. In particular, laughter has a role in stress hormone reduction, improving mood, enhancing creativity, pain reduction, improving immunity and reducing blood pressure.

TPH and suicidal behavior: a study in suicide completers. Turecki G, Zhu Z, Tzenova J, Lesage A, Seguin M, Tousignant M, Chawky N, Vanier C, Lipp O, Alda M, Joobar R, Benkelfat C, Rouleau GA Mol Psychiatry, 6(1): 98-102 2001

An association between the gene that codes for tryptophan hydroxylase (TPH) - the rate-limiting enzyme in the synthesis of serotonin - and suicidal behavior has been investigated with some detail in samples of living subjects who attempted suicide. In this study, we investigated TPH and suicide completion, the most severe form of suicidal behavior. A relatively large sample of suicide completers (n = 101) was genotyped at three TPH loci (two polymorphisms in the promoter region, A-6526G and G-5806T, and one in intron 7, A218C) and compared to psychiatrically normal living controls (n = 129). Although no significant differences were found between groups for genetic variation at single loci, haplotype analysis revealed that one haplotype (-6526G -5806T 218C) was significantly more frequent among suicide cases than in normal controls (chi(2) = 11.30, df = 2, P = 0.0008; OR = 2.0 CI: 1.30-3.6). Further analyses suggested

that this haplotype is particularly more frequent among subjects who committed suicide using violent methods. Similar results were observed in recent haplotype analyses in suicide attempters, which found that the equivalent of haplotype -6526G -5806T 218C was more frequent in impulsive attempters (Rotondo et al, Mol Psychiatry 1999; 4: 360-368). Our results replicate in suicide completers previous data observed in suicide attempters. These and other results continue to point to the substantial role that the gene that codes for TPH may play in the neurobiology of suicidal behavior.

Pharmacol Biochem Behav 2000 Dec;67(4):759-766 **Unrestricted free-choice ethanol self-administration in rats causes long-term neuroadaptations in the nucleus accumbens and caudate putamen.** Nestby P, Vanderschuren LJ, De Vries TJ, Mulder AH, Wardeh G, Hogenboom F, Schoffelmeer AN Research Institute Neurosciences Vrije Universiteit, Department of Pharmacology, Free University, Medical Faculty, Amsterdam, The Netherlands.

In the present study, the reactivity of striatal dopamine and dopamine-sensitive neurons in superfused striatal slices of ethanol-experienced rats was compared to that of ethanol-naive rats, three weeks after oral ethanol self-administration. During the acquisition phase (17 days), rats were offered increasing concentrations of ethanol (from 2 to 10%, 24 h per day) on an alternate-day schedule in a free choice with water. Following two weeks of unrestricted 10% ethanol consumption, the highest and lowest drinkers (representing about 25% of the upper and lower extremes of the total population) were selected. Preliminary experiments revealed that both groups of rats displayed a profound increase in ethanol consumption and preference three weeks after cessation of ethanol self-administration (deprivation effect). This deprivation effect was associated with an increase in electrically evoked release of [3H]dopamine from superfused nucleus accumbens slices, whereas the evoked [3H]dopamine release from caudate putamen slices remained unchanged. In slices of the caudate putamen, but not in nucleus accumbens slices, postsynaptic dopamine D1 receptor-stimulated cyclic AMP production was also enhanced. In addition, prior ethanol consumption enhanced the electrically evoked release of [14C]acetylcholine release in both striatal regions. Interestingly, the magnitude of these long-term neuroadaptations correlated with the amount of daily ethanol consumption, i.e. neuronal hyperresponsiveness in the striatum was more profound in the high than in the low ethanol drinkers. These data show for the first time that unrestricted free-choice ethanol consumption in rats is associated with a long-term increase in dopaminergic and cholinergic neurotransmission in the nucleus accumbens and caudate putamen. These (and other) neuroadaptations may underlie the enhanced motivation to self-administer ethanol and the maintenance of ethanol consumption long after deprivation.

Eur J Pharmacol 2000 Sep 29;405(1-3):303-27 **The dopamine D(4) receptor: one decade of research** Oak JN, Oldenhof J, Van Tol HH Laboratory of Molecular Neurobiology, Centre for Addiction and Mental Health, Clarke Div., 250 College Street, M5T 1R8, Toronto, Ontario, Canada.

Dopamine is an important neurotransmitter involved in motor control, endocrine function, reward, cognition and emotion. Dopamine receptors belong to the superfamily of G protein-coupled receptors and play a crucial role in mediating the diverse effects of dopamine in the central nervous system (CNS). The dopaminergic system is implicated in disorders such as Parkinson's disease and addiction, and is the major target for antipsychotic medication in the treatment of schizophrenia. Molecular cloning studies a decade ago revealed the existence of five different dopamine receptor subtypes in mammalian species. While the presence of the abundantly expressed dopamine D(1) and D(2) receptors was predicted from biochemical and pharmacological work, the cloning of the less abundant dopamine D(3), D(4) and D(5) receptors was not anticipated. The identification of these novel dopamine receptor family members posed a

challenge with respect to determining their precise physiological roles and identifying their potential as therapeutic targets for dopamine-related disorders. This review is focused on the accomplishments of one decade of research on the dopamine D(4) receptor. New insights into the biochemistry of the dopamine D(4) receptor include the discovery that this G protein-coupled receptor can directly interact with SH3 domains. At the physiological level, converging evidence from transgenic mouse work and human genetic studies suggests that this receptor has a role in exploratory behavior and as a genetic susceptibility factor for attention deficit hyperactivity disorder.

Psychosom Med 2000 May-Jun;62(3):386-93 **Active music therapy in Parkinson's disease: an integrative method for motor and emotional rehabilitation.** Pacchetti C, Mancini F, Aglieri R, Fundaro C, Martignoni E, Nappi G Parkinson's Disease and Movement Disorders Centre, Istituto di Ricerca e Cura a Carattere Scientifico C. Mondino, University of Pavia, Italy.

BACKGROUND: Modern management of Parkinson's disease (PD) aims to obtain symptom control, to reduce clinical disability, and to improve quality of life. Music acts as a specific stimulus to obtain motor and emotional responses by combining movement and stimulation of different sensory pathways. We explored the efficacy of active music therapy (MT) on motor and emotional functions in patients with PD. **METHODS:** This prospective, randomized, controlled, single-blinded study lasted three months. It consisted of weekly sessions of MT and physical therapy (PT). Thirty-two patients with PD, all stable responders to levodopa and in Hoehn and Yahr stage two or three, were randomly assigned to two groups of 16 patients each. We assessed severity of PD with the Unified Parkinson's Disease Rating Scale, emotional functions with the Happiness Measure, and quality of life using the Parkinson's Disease Quality of Life Questionnaire. MT sessions consisted of choral singing, voice exercise, rhythmic and free body movements, and active music involving collective invention. PT sessions included a series of passive stretching exercises, specific motor tasks, and strategies to improve balance and gait. **RESULTS:** MT had a significant overall effect on bradykinesia as measured by the Unified Parkinson's Disease Rating Scale ($p < .034$). Post-MT session findings were consistent with motor improvement, especially in bradykinesia items ($p < .0001$). Over time, changes on the Happiness Measure confirmed a beneficial effect of MT on emotional functions ($p < .0001$). Improvements in activities of daily living and in quality of life were also documented in the MT group ($p < .0001$). PT improved rigidity ($p < .0001$). **CONCLUSIONS:** MT is effective on motor, affective, and behavioral functions. We propose active MT as a new method for inclusion in PD rehabilitation programs.

Percept Mot Skills 2000 Feb;90(1):307-14 **Effects of music on mood during bench stepping exercise.** Hayakawa Y, Miki H, Takada K, Tanaka K Yamano College of Aesthetics, Tokyo, Japan.

This study evaluated the effect of music on the mood of women during exercise. Sixteen middle-aged women, aged 49.9 – 75.3 yr., performed 60-min. bench stepping exercise while listening to Japanese traditional folk song, aerobic dance music, or nonmusic. The subjects reported significantly less fatigue with aerobic dance music and Japanese traditional folk song than with nonmusic. Aerobic dance music was associated with significantly more vigor and less confusion than nonmusic.

J Psychiatr Ment Health Nurs 1998 Oct;5(5):403-8 **Objective measurement of mood change induced by contemporary music.** Smith JL, Noon J Maudsley Hospital, London, UK.

A myriad of previous studies from a variety of disciplines has shown several effects of music on mind and body. This study investigated the relationship between different categories of contemporary music (n = 6) and the mood states of a group of students (n = 12), using the Profile of Mood States (POMS), to measure mood before and after exposure to these different pieces of music. When analyzed together, all six pieces of music produced an overall change in mood (P = 0.008) as measured by 2way repeated measures analysis of variance (ANOVA). When each category was examined individually, four categories of music produced highly significant changes in mood: the tense category (score -4.0 +/- 1.8 POMS Units; P < 0.001); depressed category (+0.5 +/- 0.2; P < 0.001); angry category (+0.9 +/- 1.6; P < 0.03); and the all moods category (1.6 +/- 0.3; P < 0.04). One piece of dance music produced changes in all mood categories, giving the largest positive mean mood change. By contrast, the popular/independent music, associated with the tense category, produced the largest negative mean mood change. The five POMS mood states were analyzed separately for each piece of music. These findings are consistent with previous work. In addition, the finding of the effects of specific music categories on mood may have important implications for therapy in mental health and mental health nursing.

Kaye WH, Greeno CG, Moss H, Fernstrom J, Fernstrom M, Lilienfeld LR, Weltzin TE, Mann JJ **“Alterations in serotonin activity and psychiatric symptoms after recovery from bulimia nervosa.”** Arch Gen Psychiatry 1998 Oct;55(10):927-35 Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, PA 15213, USA.

BACKGROUND: Women with bulimia nervosa (BN) have disturbances of mood and behavior and alterations of monoamine activity when they are bingeing and purging. It is not known whether these alterations are secondary to pathological eating behavior or traits that could contribute to the pathogenesis of BN. **METHODS:** To avoid the confounding effects of pathological eating behavior, we studied 30 women after long-term recovery (>1 year with no bingeing or purging, normal weight, and regular menstrual cycles) from BN. Subjects were compared with 31 healthy volunteer women. We assessed psychiatric diagnoses and symptoms to determine whether there was any persistent disturbance of behavior after recovery. We measured cerebrospinal fluid (CSF) levels of the major metabolites of serotonin (5-hydroxyindoleacetic acid [5-HIAA]), dopamine (homovanillic acid [HVA]), and norepinephrine (3-methoxy-4-hydroxyphenylglycol [MHPG]) as well as hormonal and behavioral response to mchlorophenylpiperazine (m-CPP), a serotonin-specific agent.

RESULTS: Women who were recovered from BN had mild to moderate negative moods and obsessions with perfectionism and exactness and exaggerated core eating disorder symptoms compared with healthy volunteer women. Recovered BN women had increased levels of CSF 5HIAA compared with control women (117 +/- 33 vs 73 +/-15 pmol/mL; P < or =.001) but normal CSF HVA and MHPG concentrations. Recovered BN women had an anxious and disorganized behavioral response to m-CPP but a normal hormonal response. **CONCLUSIONS:** Persistent serotonergic and behavioral abnormalities after recovery raise the possibility that these psychobiological alterations might be trait-related and contribute to the pathogenesis of BN.

McDougle CJ, Epperson CN, Price LH, Gelernter J **“Evidence for linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and obsessive compulsive disorder.”** Mol Psychiatry 1998 May;3(3):270-3 Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA.

Obsessive compulsive disorder (OCD) is characterized by recurrent and intrusive thoughts that are distressing (obsessions) and/or repetitive behaviors or mental acts that the person feels driven to perform (compulsions). OCD has a partly genetic basis. For treatment of OCD, potent serotonin reuptake inhibitor (SRI) drugs (clomipramine (Anafranil), fluvoxamine (Luvox), fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil)), which act on the serotonin transporter protein, are uniquely efficacious. A polymorphism in the promoter region of the gene (SLC6A4) encoding this protein, was recently reported to affect protein expression and to be associated with measures of anxiety and depression and with autism (using a family-controlled transmission disequilibrium test (TDT) design). SLC6A4 therefore has strong a priori support for potentially influencing risk for OCD: the protein it encodes is a medication target; a polymorphism in the gene affects function; and that polymorphism has been shown to be associated with behavioral phenotypes. We used the TDT with a set of 34 European-American family trios, 30 unrelated and four drawn from an extended pedigree, to test for linkage disequilibrium between OCD and alleles at the SLC6A4 promoter polymorphic locus. Of 35 heterozygous parents, 24 transmitted the 'l' SLC6A4 allele and 11 transmitted the 's' allele (χ^2 TDT = 4.83; $P < 0.03$). Considering only the 13 SRI drug nonresponders, there were 13 heterozygous parents, of whom 10 transmitted the 'l' allele and three the 's' allele (χ^2 TDT = 3.77; $P < 0.052$). These data provide preliminary support for association and linkage disequilibrium between the SLC6A4 'l' allele and OCD.

Hanna GL, Himle JA, Curtis GC, Koram DQ, Weele JV, Leventhal BL, Cook EH Jr **“Serotonin transporter and seasonal variation in blood serotonin in families with obsessive-compulsive disorder.”** Neuropsychopharmacology 1998 Feb;18(2):102-11 Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109-0390, USA.

The serotonin transporter (HTT) is a candidate gene for obsessive-compulsive disorder (OCD) that has been associated with anxiety-related traits. The long (l) and short (s) variants of the HTT promoter have different transcriptional efficiencies. HTT promoter genotype and blood 5-HT concentration were examined in 70 subjects from 20 families ascertained through children and adolescents with a DSM-III-R diagnosis of OCD. The HTT promoter variant had a significant effect on blood 5-HT content. Subjects with the l/l and l/s genotypes had significantly higher blood 5-HT levels than did those with the s/s genotype. There was a significant interaction between HTT promoter genotype and seasonal variation in blood 5-HT content, with significant seasonal differences in 5-HT occurring only in the subjects with the l/l genotype. Further studies of the regulation of HTT gene expression are indicated.

Oncol Nurs Forum 1997 May;24(4):663-71 **Spiritual well-being, religiosity, hope, depression, and other mood states in elderly people coping with cancer.** Fehring RJ, Miller JF, Shaw C Marquette University in Milwaukee, WI, USA.

PURPOSE/OBJECTIVES: To determine the relationships among spiritual well-being, religiosity, hope, depression, and other mood states in elderly people coping with cancer and if differences in hope, depression, and other mood states exist between those elderly with high and low intrinsic religiosity and spiritual well-being. **DESIGN:** Descriptive correlational and descriptive comparison. **SETTING:** Acute care units of two hospitals located in the midwestern United States. **SAMPLE:** 100 elderly people with diagnosis of cancer and a mean age of 73 years. Thirty-three of the subjects were male, and 67 were female. Sixty-two percent had either lung,

breast, or colon cancer. **METHODS:** Each subject was administered an intrinsic and extrinsic religiosity index, a spiritual well-being scale, a geriatric depression scale, the Miller hope scale, and the Profile of Mood States scale. **MAIN RESEARCH VARIABLES:** Spiritual well-being, religiosity, hope, depression, and mood. **FINDINGS:** A consistent positive correlation was found among intrinsic religiosity, spiritual wellbeing, hope, and other positive mood states. A consistent negative correlation among intrinsic religiosity, depression, and other negative mood states existed. Analysis of variance indicated that significantly higher levels of hope and positive moods existed in elderly patients with high levels of intrinsic religiosity and spiritual well-being. **CONCLUSION:** Intrinsic religiosity and spiritual wellbeing are associated with hope and positive mood states in elderly people coping with cancer. **IMPLICATIONS FOR NURSING PRACTICE:** Nurses must assess and support intrinsic religiosity and promote spiritual well-being in elderly people coping with cancer.

Sasson Y, Zohar J **“New developments in obsessive-compulsive disorder research: implications for clinical management.”** Int Clin Psychopharmacol 1996 Dec;11 Suppl 5:3-12 Department of Psychiatry, Chaim Sheba Medical Center, Sackler Medical School, Tel Aviv University, Israel.

Over the past decade, epidemiological, phenomenological, pharmacological, neurobiological, brain imaging and genetic research has contributed to a substantial change in our understanding of obsessive-compulsive disorder (OCD). Once regarded as a rare psychodynamic illness, OCD is now recognized as a common condition affecting 2-3% of the population. Better recognition combined with the demonstrated efficacy of serotonin reuptake inhibitors, such as clomipramine and the selective serotonin reuptake inhibitors (SSRIs), has dramatically improved the prognosis of this disorder, which exacts a considerable personal and economic burden. While the aetiology is still not understood, increasingly sophisticated research techniques are enabling us to begin to uncover the underlying pathophysiology of this illness. This paper reviews some of the recent developments which have enhanced our understanding of OCD and considers their potential impact on clinical management.

Psychol Med 1996 Mar;26(2):323-31 **Aggression and personality: association with amino acids and monoamine metabolites.** Moller SE, Mortensen EL, Breum L, Alling C, Larsen OG, Boge-Rasmussen T, Jensen C, Bennicke K Research Institute of Biological Psychiatry, St Hans Hospital, Roskilde, Denmark.

Associations in 52 normal individuals were examined between plasma and cerebrospinal fluid (CSF) concentrations of tryptophan (Trp) and tyrosine, and concentrations of monoamine metabolites in the CSF, and scores on an aggression questionnaire, the Kinsey Institute Reaction List II, and the Eysenck Personality Questionnaire. There was a significantly positive correlation between CSF 5hydroxyindoleacetic acid (5-HIAA) levels and extroverted aggression scores, and a significantly negative correlation between CSF 5-HIAA levels and introverted aggression scores. Males showed higher plasma Trp concentrations than females, and significantly positive correlations between plasma Trp concentrations and scores on extroverted aggression and the Eysenck E scale. Males, furthermore, showed a significantly negative correlation between CSF Trp levels and scores on the Eysenck P scale, and a significantly positive correlation between concentrations of 3-methoxy-4-hydroxy-phenylglycol in CSF and scores on moral aggression. These results suggest that central serotonin influences aggression in normal individuals through effects on personality.

J Neural Transm 1976;39(3):257-67 **Serotonin, noradrenaline, dopamine metabolites in transcendental meditation-technique.** Bujatti M, Riederer P

The highly significant increase of 5-HIAA (5-hydroxyindole-3-acetic acid) in Transcendental Meditation technique suggests systemic serotonin as "rest and fulfillment hormone" of deactivation-relaxation. Furthermore 5-HT (5-hydroxytryptamine, serotonin) is considered to be the EC-cell (enterochromaffine-cell) hormone requested by Fujita and Kobayashi and its role for EEG synchronisation via area postrema chemoreceptor as anti arousal agent is being discussed. The significant decrease of the catecholamine metabolite VMA (vanillic-mandelic acid) in meditators, that is associated with a reciprocal increase of 5-HIAA supports as a feedback necessity the "rest and fulfillment response" versus "fight and flight." As the adreno medullary tissue serves for hormonal reinforcement of orthosympathetic activity, the Enterochromaffine Cell System (having taken the form of distinct organs in some species as octopus and discoglossus) is suggested to serve via serotonin for humoral reinforcement of parasympathetic activity in deep relaxation.

Vanderschuren LJ, Kalivas PW **Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies.** Research Institute Neurosciences Vrije Universiteit, Department of Pharmacology, Medical Faculty, Free University, Amsterdam, The Netherlands.

RATIONALE AND OBJECTIVES: Repeated exposure to many drugs of abuse results in a progressive and enduring enhancement in the motor stimulant effect elicited by a subsequent drug challenge. This phenomenon, termed behavioral sensitization, is thought to underlie certain aspects of drug addiction. Behavioral sensitization is the consequence of drug-induced neuroadaptive changes in a circuit involving dopaminergic and glutamatergic interconnections between the ventral tegmental area, nucleus accumbens, prefrontal cortex and amygdala.
METHODS: The literature was critically reviewed in an effort to discern the relative roles of glutamate and dopamine transmission in the induction and expression of sensitization to amphetamine, cocaine and mu-opioids. In addition, the literature was reviewed to evaluate distinctions between these drugs in the involvement of the relevant brain nuclei listed above.
RESULTS: The common substrates between sensitizing drugs are glutamate transmission, especially at the NMDA receptor, and an action in the ventral tegmental area. In contrast, a role for dopamine is only clearly seen in amphetamine sensitization and critical involvement of nuclei outside the ventral tegmental area is found for cocaine and morphine. While enhanced dopamine transmission is associated with sensitization by all three drugs, a role for glutamate is clearly identified only with cocaine sensitization. Accordingly, glutamatergic cortical and allocortical brain regions such as the prefrontal cortex appear more critical for cocaine sensitization.
CONCLUSIONS: The distinctions between drugs in the induction and expression of sensitization indicate that behavioral sensitization can arise from multiple neuroadaptations in multiple brain nuclei. This is not only the result of distinct molecular targets for the drugs, but may also include a differential involvement of learned associations. It is postulated that the relatively more robust pharmacological capacity of amphetamine to release dopamine may induce a form of sensitization that is more dependent on adaptations in mesoaccumbens dopamine transmission compared with cocaine and morphine sensitization

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