3

BRAIN TRYPTOPHAN

Normal and Disturbed Control

G. Curzon

Institute of Neurology
Queen Square
London, WC 1N 3BG, United Kingdom

1. INTRODUCTION

I am both pleased and honoured to have been invited to lecture here where the modern age might reasonably be said to have begun. It was in Padua that Galileo wrote a book, Siderius Nuncius - in English, "The Messengers of the Stars" - which set the seal on a revolution in how we visualise the Universe and our place in it. I am also pleased to be at a place that has had a great influence on British scolarship - where William Harvey was led towards discovering the circulation of the blood and where the English ambassador to Venice, Sir Henry Wotton was so involved with its intellectual life that he sent Galileo's Messenger of the Stars to King James the First on its actual day of publication (13/3/1610). The covering letter (quoted by Smith, 1907) is quite amusing; Wotton is impressed but cautious and dismisses science in favour of more important matters.

"I send — his Majesty the strangest piece of news — that he hath ever yet received— [a book published] this very day of the Mathematical Professor at Padua, who by the help of an optical instrument— hath overthrown all former astronomy —[and] must become either exceeding famous or exceeding ridiculous. Now to descend from these novelties to those which do more concern the wise men of this place." Wotton then goes on to discuss political topics.

It is also a pleasure to be invited to give a plenary lecture at ISTRY as I have attended all the ISTRY meetings since the first one held here 21 years ago and I have been involved in some way with tryptophan (TRP) since 1948 when I began working for a PhD at Leeds in the Biochemistry Department then chaired by Professor Frank Happold. His main interest at that time was the bacterial enzyme tryptophanase which hydrolyses TRP into indole and serine. My PhD was not on this topic but I must have breathed in an awareness of TRP. Rather similarly, when years later, Simon Young the present President of the executive committee of ISTRY, did his PhD at my laboratory, in London at the Institute of Neurology, though he did not work on TRP, he also seems to have suffered an air-borne infection with it.

The pattern of my own work was largely determined back in 1964 by John Cumings when I was a junior member of his department at the Institute of Neurology. Cumings had

Recent Advances in Tryptophan Research, edited by Graziella Allegri Filippini et al.
Plenum Press, New York, 1996

planned a book on biochemical aspects of neurology and psychiatry to be based on a series of lectures. When he told me that I was to do the one on the biochemistry of depression I said that it was a subject I knew nothing about. He replied: "well you will have to go off and find out," which was how I first heard about the liver enzyme TRP 2,3-dioxygenase, (then called TRP pyrrolase) and had what I then thought was an original idea on how depression might be precipitated, i.e that an "alteration of TRP metabolism occurs [in depression] of which 5-hydroxytryptamine changes are a part. [As] the main pathway of TRP metabolism by TRP pyrrolase to kynurenine, etc. is increased by stress — it may be that the result of long periods of stress is the diversion of TRP from the 5-hydroxytryptamine— pathways to the kynurenine pathway" (Curzon, 1965).

Similar ideas were in fact proposed by a number of people around that time (see Curzon, 1969 for references). Examples were subsequently reported of reciprocal associations between activity of the liver enzyme and brain TRP concentration (e.g. Badawy et al., 1989; Litman and Correia, 1985) and recently developed inhibitors of the enzyme have been shown to strikingly increase central TRP concentration (Salter et al., 1995). However, though there is now substantial evidence of moderate TRP deficiency in depression, how it occurs and how important it is in the illness remain incompletely resolved questions (see below). Much of the work of my own laboratory on the *normal* control of brain TRP and the effect of TRP on 5-HT synthesis was first stimulated by the interest in these questions.

2. NORMAL CONTROL OF BRAIN TRP

When we began our work in 1965 there was what now seems surprisingly little interest in the influence of TRP availability on brain 5-HT synthesis. Eccleston et al. (1965) had reported in the same year that TRP increased rat brain 5-HT and its metabolite 5-HIAA but they had used very large doses of amino acid so that brain TRP rose far beyond the physiologically relevant range. It was only later that work on the effects of dietary intake on brain TRP concentration was stimulated by the important studies of Fernstrom and Wurtman (1971, a,b) on the effect on brain 5-HT synthesis of relatively small changes of TRP availability. At about the same time, we were depriving rats of food for 24 hr, expecting that brain TRP and hence 5-HT synthesis would decrease. Instead they both increased (Curzon et al., 1972) as fasting elevated plasma unesterified fatty acid which freed plasma TRP from albumin so that it became more available to the brain (Knott and Curzon, 1972). This findings, together with the increase of brain TRP after a single large TRP-free high carbohydrate meal (Fernstrom and Wurtman, 1972) which also might have been expected to decrease it, imply that the brain is effectively protected in these rather extreme circumstances against low TRP intake. Similarily, intrauterinally malnourished newborn rats have raised brain TRP values and corresponding humans have raised plasma free TRP concentrations and raised plasma ratios of free (but not of total) TRP to the sum of the large neutral amino acids (LNAAs) which compete with it for transport to the brain (Hernandez et al., 1989).

In an investigation on the dietary control of human plasma TRP, Eriksson et al. (1989) found that TRP/LNAA ratios in subjects on standard hospital meals only varied slightly over a 24 hr period. In related animal work, exposure of rats to diets od 0-40% protein for 2 hr after 12 hr food deprivation had only moderate effects on brain TRP concentration and though there was a significant correlation between plasma total TRP/LNAA ratios and brain TRP this only accounted for 20% of the variance of the brain values (Voog and Eriksson, 1992). Predictability of brain values from plasma ratios was increased in studies in which calculations were based on plasma free TRP (Smith et al., 1987., Takada et al., 1993). Similarly, plasma free TRP appeared to be the form of the amino acid that was most readily available

to the human brain (Gillman et al., 1981., Delgado et al., 1990; Cangiano et al., 1990). Other workers reported that quite wide human dietary variation had little effect on total plasma TRP/LNAA ratios (Fernstrom, 1987) and human CSF TRP and 5-HIAA concentrations were unaffected by protein or carbohydrate breakfasts (Teff et al.1989). These findings are consistent with the stability of brain amino acid pools under many conditions (Harper and Tews, 1988).

However, more extreme influences can increase brain TRP e.g. prolonged exercise (Chaouloff, 1989; Wilson and Marsden, 1993) via increased plasma free TRP; immobilization by enhancing the kinetics of TRP transport to the brain (Kennett et al., 1986); a large high carbohydrate meal by decreasing the plasma concentrations of other LNAAs (Fernstrom and Wurtman, 1971; Sarna et al., 1985); ageing by a combination of these influences (Sarna et al., 1982). It is remarkable that brain TRP increases in so many circumstances but resists decraese except on prolonged malnourishment (Dickerson and Pao, 1975; Fernstrom and Hirsch, 1977) or pharmacological treatments.

The kinetics of transport of TRP across the blood-brain barrier vary with species (Pardridge and Fierer, 1990). Enhanced transport during immobilization stress (Kennett et al., 1986) is propably due to action of secreted catecholamine at β-adrenergic receptors (Dunn and Welch, 1991), the brain appearing to strip TRP from its binding to albumin under these conditions.

3. DISTURBED CONTROL OF BRAIN TRP

3.1 Depression

Evidence on the availability of TRP to the brain in depressive illness is mostly based on plasma determinations. Low plasma free TRP in depression was first reported by Coppen et al. (1973) and confirmed by DeMyer et al. (1981) and Schmid-Burgk et al. (1981). Unlike the other two groups, DeMyer et al. also found low plasma total TRP as did Joseph et al. (1984) Lucca et al. (1992) and Karege et al. (1994). These three groups did not report free TRP data. Coppen, DeMyer, Karege and their co-workers all found that values returned to normal on recovery. Moller et al. (1979) obtained normal plasma TRP concentrations but Moller et al. (1990) later reported that lower TRP or TRP/LNAA values predicted % improvement on treatment with 5-HT reuptake inhibitors. Mathis et al. (1988) also found normal TRP but reported low TRP/LNAA values. Taken together, these results strongly suggest that low availability of plasma TRP to the brain is associated with depressive symptoms. Whether it has some responsability for them is another question though the reversal of the antidepressant effect of 5-HT reuptake inhibitors when plasma TRP is rapidly decreased by an oral load of LNAAs (Delgado et al., 1990) is suggestive.

There are also reports on subjects with postpartum depression of low plasma free (but not total) TRP (Stein et al., 1976), low plasma total TRP/LNAA ratios (Maes et al.,1992) and absence of the normal postpartum rise in plasma TRP (Handley et al., 1980). The exacerbation of premenstrual depression and irritability when plasma TRP is rapidly decreased by oral LNAA loading (Menkes et al., 1994) is also of interest. However, low plasma TRP may be related to retarded affect rather than to depressive illness as such as both total and free values of a group of patients with high retardation scores were significantly low independently of their final diagnoses (Curzon et al., 1979). It is also worth noting that subjects without significant anxiety or depression but with presumed stress as they were full-time carers of patients with Alzheimer's disease had low plasma free (but not total) TRP (Hockney et al., 1992).

The following observations point to different (but not necessarily mutually exclusive) ways low plasma TRP could occur in depression.

a. *Enhanced metabolism, enhanced uptake by tissues or defective absorption.* Mechanisms of this kind are indicated by the relatively small rises of plasma TRP after oral loading (Russ et al., 1990). Enhanced metabolism is suggested by the high urinary excretion of metabolites on the tryptophan-2,3-dioxygenase or indoleamine-2,3-dioxigenase (IDO) pathways (Curzon and Bridges, 1970; Maes et al., 1987). Increased metabolism by indoleamine-2,3-dioxygenase is conceivably consistent with various indices of altered immune function that are reported to correlate with the low TRP values (Maes et al., 1993).
b. *Effects of loss of appetite.* This is suggested by reports that low plasma TRP in depression was associated with both female sex and low body weight (Anderson et al., 1990) and that plasma TRP decreased in normal women (but not men) after 3 weeks of moderate dieting (Walsh et al., 1995).

Low plasma TRP in depression is paralleled to some extent by CNS findings. Inefficient uptake of plasma TRP by the brain is perhaps suggested by PET scan studies showing abnormally low uptake of the related amino acid. [^{1}C]-5-HTP when given intravenously (Agren et al., 1991). Also, TRP concentrations in lumbar CSF were found to be low by Coppen et al. (1972) though this was not confirmed by Ashcroft et al. (1993) and Banki et al. (1981) was unable to show significant correlations between lumbar values and intensity of symptoms.

That low brain TRP concentrations would lead not only to low concentrations of 5-HT in brain tissue but also to low concentrations at receptors is indicated by in vivo dialysis studies on rats with TRP availability to the brain impaired by administration of LNAAs (Heslop et al., 1991; Gartside et al., 1992).

3.2 Appetite Disorders

Starvation can cause anorexia (Hunsicker et al., 1992), and appetite is impaired by activation of hypothalamic postsynaptic 5-HT receptors (rev. Curzon et al., 1993). Therefore, the rise of brain TRP concentration and 5-HT metabolism on 24 hr food deprivation (Curzon et al., 1972); Fuenmayor and Garcia, 1984) is of interest with respect to anorexia nervosa especially as in vivo dialysis data suggests that the increase of 5-HT at receptors in the lateral hypothalamus on giving TRP is greater after food deprivation (Schwartz et al. 1990). In normal subjects, any appetite suppressant effect of this increase is presumably effectively opposed by appetite stimulation by other substances released on deprivation e.g. neuropeptide Y (Lambert et al., 1994) and noradrenaline (Stanley et al., 1989). However, it is conceivable that in some subjects the 5-HT changes are dominant and lead to anorexia nervosa. Such changes might well be provokable by slimming regimes and exacerbated by stress (Knott et al., 1977). It is relevant that female but not male volunteers on low calorie intake have an increased 5-HTergic response to tryptophan as indicated by the rise of plasma prolactin on TRP loading (Goodwin et al., 1987) though whether this reflects enhanced hypothalamic 5-HT function or altered availability of the TRP load to the brain is not entirely clear (Anderson et al., 1990). Cancer anorexia could also involve increased 5-HT function as plasma free TRP and CSF TRP both increase (Cangiano et al., 1990). However, the hypothesis for precipitation of anorexia nervosa through excessive release of 5-HT to receptors is not strengthened by data on subjects with established anorexic illness as evidence pointing to increased brain 5-HT is lacking (Ploog and Pirke, 1987). On the other hand, metabolic abnormalities resulting from the illness make interpretation difficult.

Increased urge to eat appears to be diametrically opposite to anorexia, though subjects can fluctuate between anorexia nervosa and bulimia nervosa (i.e. weight control by self-induced

vomiting after binge eating). However, there is some evidence of contrasting neurochemical abnormalities in the two conditions as bingeing terminates when plasma TRP/LNAA ratios rise (Kaye et al., 1988) so that brain 5-HT synthesis presumably increases. This agrees with the causal role for defective hypothalamic 5-HT function in the illness which is indicated by reduced prolactin responses to 5-HTergic drugs (Brewerton et al., 1992; Jimerson et al., 1994).

3.3 Other Disturbances

Brain TRP changes have been described in a number of the other disorders. A large and proliferating literature now exists on the enhanced induction of IDO in a wide range of inflammatory neurological disorders with excessive production of potentially neurotoxic quinolinic acid (e.g. Heyes et al., 1992; Holzman, 1993). Justice cannot be done to this topic within the scope of the present lecture.

There is also a substantial literature on the increase of brain TRP and 5-HT metabolism in human and experimental (shunt) liver failure (e.g. Record et al., 1976; Bloxam and Curzon, 1978; Bengtsson et al., 1991). The TRP changes are explicable partly by a rise of plasma free TRP and partly by increased uptake across the blood-brain barrier (Bloxam and Curzon, 1978) which is, in turn, at least in part, dependent on hyperammonaemia (Jessy et al., 1990). Brain 5-HT metabolism increases largely as a result of the rise of brain TRP though increases of tryptophan hydroxylase activity are also reported in some brain regions (Bengtsson et al., 1991). Resultant increases of the availability of 5-HT to receptors could conceivably be implicated in the development of symptoms. However, recent in vivo dialysis experiments indicate that 5-HT release did not increase on chronic liver failure and decreased on acute shunt (Bergqvist et al., 1995). This finding suggests that the symptoms of hepatic encephalopathy may not involve increased 5-HT release. Whether these symptoms and those associated with hyperammonaemia depend on increased production of quinolinic acid is controversial (Robinson et al., 1992).

Increased brain TRP and 5-HT metabolism are also indicated in human renal disease with encephalopathy (Sullivan et al., 1980) as CSF TRP and 5-HIAA both rose. The central changes were explicable by increased plasma free TRP and were reversed by kidney dialysis (Sullivan et al., 1980).

REFERENCES

Agren, H., Reibring, L., Hartvig P., Tedroff, J., Bjurling, P.,Hornfeldt, K., Andersson, Y., Lundqvist, H. and Langstrom, B., 1991, Low brain uptake of L-[^{11}C]5-hydroxytryptophan in major depression: a positron emission study on patients and healthy volunteers., *Acta Psychiat. Scand.*, 83: 449.

Anderson, I.M., Parry-Billings, M., Newsholme, E.A., Poortmans, J.R., and Cowen, P. J., 1990, Decreased plasma tryptophan concentration in major depression : relationship to melanchonia and weight loss, *J.Affect.Dis.*, 20:185.

Anderson, I.M., Parry-Billings, M., Newsholme, E.A., Fairburn, C.G., and Cowen P.J., 1990, Dieting reduces plasma tryptophan and alters brain 5-HT function in women, *Psychol. Med.*, 20: 785.

Ashcroft, G.W., Blackburn, I.M., Eccleston, D., Glen, A.I.M., Hartley, W., Kinloch, N.E., Lonergan, M., Murray, L.G., and Pullen, I.A., 1973, Changes on recovery in the concentartion of tryptophan and the biogenic amine metabolites in the cerebrospinal fluid of patients with affective illness, *Psychol. Med.*, 3: 319.

Badawy, A.A-B., Morgan, C.J., Lane, J., Dhaliwal, K., and Bradley, D.M., 1989, Liver tryptophan pyrrolase. A major determinant of the lower brain 5-hydroxytryptamine concentration in alcohol-preferring C57BL mice, *Biochem. J.* 264: 597.

Banki, C.M., Vojnik, M., and Molnar, G., 1981, Cerebrospinal fluid amine metabolites, tryptophan and clinical parameters in depression, *J.Affect., Dis.*, 3:81.

Bengtsson, F., Bugge, M., Johansen, K.H., and Butterworth, R.F., 1991, Brain tryptophan hydroxylase in the portocaval shunted rat: a hypothesis for the regulation of serotonin, *J.Neurochem.*, 56: 1069.

Bergqvist, P.B.F., Vogels, B.A.P.M., Bosman, D.K., Maas, M.A.W., Hjorth, S., Chamuleau, R.A.F.M., and Bengtsson, F., 1995, Neocortical dialysate monoamines of rats after acute, subacute and chronic liver shunt, *J.Neurochem.* 64: 1238.

Bloxam, D.L. and Curzon, G., 1978, A study of proposed determinants of brain tryptophan concentration in rats after portocaval anastomosis or sham operation, *J.Neurochem.*, 31:1255.

Brewerton, T.D., Mueller, E.A., Lesem, M.D., Brandt, H.A., Querry, B., George, D.T., Murphy, D.L., and Jimerson, D.C., 1992, Neuroendocrine response to m-chlorophenylpiperazine and L-tryptophan in bulimia, *Arch. Gen. Psychiat.*, 49: 852.

Cangiano, C., Cascino, A., Ceci, F., Laviano, A., Mullerl, M., Muscaritoll, M., and Rossi-Fanelli, F., 1990, Plasma and CSF tryptophan in cancer anorexia, *J.Neural.Transm.* [Gen Sect.], 81 : 225.

Chaouloff, F., Kennett, G.A., Serrurrier, B., Merino, D., and Curzon, G., 1986, Amino acid analysis demonstrates that increased plasma free tryptophan causes the increase of brain tryptophan during exercise in the rat, *J.Neurochem.*, 46: 1647.

Coppen, A., Brooksbank, B.W.L., and Peet, M., 1972, Tryptophan concentration in the cerebrospinal fluid of depressive patients, *Lancet*, 1:1393.

Coppen, A., Eccleston, E.G., and Peet, M., 1973, Total and free tryptophan concentration in the plasma of depressive patients, *Lancet*, ii: 60.

Curzon, G., 1965, The biochemistry of depression in :"Biochemical Aspects of Neurological Disorders, 2nd series" J.N.Cumings and M.Kremer, eds., Blackwell, Oxford, pp257.

Curzon, G., 1969, Tryptophan pyrrolase- a biochemical factor in depressive illness?, *Br.J.Psychiat.*, 115: 1367.

Curzon, G., and Bridges, P.K., 1970, Tryptophan metabolism in depression, *J.Neurol. Neurosurg. Psychiat.*, 33: 698.

Curzon, G., Joseph, M.H. and Knott, P.J., 1972, Effcets of immobilization and food deprivation on rat brain tryptophan metabolism, *J.Neurochem.*, 19: 1967.

Curzon, G., Kantamaneni, B.D., Lader, M.H., and Greenwood, M.H., 1979, Tryptophan disposition in psychiatric patients before and after stress, *Psychol.Med.*, 9:457.

Curzon, G., Kantamaneni, B.D., Van Boxel, P., Gillman, P.K., Bartlett, J.R. and Bridges, P.K., 1980, Substances related to 5-hydroxytryptamine in plasma and in lumbar and ventricular fluids of psychiatric patients, *Acta Psychiat., Scand.* 61 Suppl. 280:3.

Curzon, G., Gibson, E.L., Kennedy, A.J., and Oluyomi, A.D., 1993, Serotoninergic pharmacology of appetite, in "Serotonin. From cell biology to pharmacology and therapeutics", P.M. Vanhoutte, P.R. Saxena, R.Paoletti, and N.Brunello, eds., Kluwer, Dordrecht, pp 393.

Delgado, P.L., Charney, D.S., Price, L.H., Aghajanian, G.K., Landis, H., and Heninger, G.R., 1990, Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan, *Arch.Gen.Psychiat.*, 47:411.

De Myer, M.K., Shea, P.A., Hendrie, H.L., and Yoshimura, N.N. 1981, Plasma tryptophan and five other amino acids in depressed and normal subjects, *Arch.Gen.Psychiat.*, 38:642.

Dickerson, J.W.T., and Pao, S-K., 1975, The effect of a low protein diet and exogenous insulin on brain tryptophan and its metabolites in the weanling rat, *J. Neurochem.*, 25:555.

Dunn, A.J., and Welch, J., 1991, Stress-and endotoxin-induced increases in brain tryptophan and serotonin metabolism depend on sympathetic nervous system activity, *J.Neurochem.*, 57: 1615.

Eccleston, D., Ashcroft, G.W., and Crawford, T.B.B., 1965, 5-Hydroxyindole metabolism in rat brain. A study of intermediate metabolism using the technique of tryptophan loading-II, *J.Neurochem.*, 12:493.

Eriksson, T., Voog, L., Walinder, J., and Eriksson, T.E. 1989, Diurnal rhythm in absolute and relative concentrations of large neutral amino acids in human plasma, *J. Psychiat. Res.*, 23:241.

Fernstrom, J.D., 1987, Food induced changes in brain serotonin synthesis: is there a relationship to appetite for specific macronutrients?, *Appetite*, 8:163.

Fernstrom, J.D., and Hirsch, M.J., 1977, Brain serotonin synthesis: reduction in corn-malnourished rats, J. *Neurochem.*, 28:877.

Fernstrom, J.D., and Wurtman, R.J. 1971a, Brain serotonin content: physiological dependence on plasma tryptophan levels, *Science*, 173: 249.

Fernstrom, J.D., and Wurtman, R.J., 1971b, Brain serotonin content : increase following ingestion of carbohydrate diet, *Science*, 174: 1023.

Fernstrom, J..D., and Wurtman, R.J., 1972, Brain serotonin content: physiological regulation by plasma neutral amino acids, *Science*, 178: 414.

Fuenmayor, L.D., and Garcia, S., 1984, The effect of fasting on 5-hydroxytryptamine metabolism in brain regions of the albino rat, *Br.J.Pharmacol.*, 83:357.

Gartside, S.E., Cowen, P.J., and Sharp, T.,1992, Evidence that the large neutral amino acid L-valine decreases electrically-evoked release of 5-HT in the hippocampus, *Psychopharmacology*, 109:251.

Gillman, P.K., Bartlett, J.R., Bridges, P.K., Hunt, A., Patel, A.J., Kantamaneni, B.D., and Curzon, G., 1981, Indolic substances in plasma, cerebrospinal fluid, and frontal cortex of human subjects infused with saline or tryptophan, *J.Neurochem.*, 37: 410.

Goodwin, G.M., Fairburn, C.G., and Cowen, P.J., 1987, The effect of dieting and weight loss on neuroendocrine responses to tryptophan, clonidine and apomorphine in volunteers, *Arch. Gen. Psychiat.*, 44:952.

Handley, S.L., Dunn, T.L., Waldron, G., and Baker, J.M., 1980, Tryptophan, cortisol and puerperal mood, *Br.J.Psychiat.*, 136:498.

Harper, A.E., and Tews, J.K., 1988, Nutritional and metabolic control of brain amino acid concentrations, In:"Amino acid availability and brain function in health and disease". G.Huether, ed., Springer, Berlin, pp3.

Hernandez, J., Manjarrez, G.G., and Chagoya, G., 1989, Newborn humans and rats manourished in utero: free plasma L-tryptophan, neutral amino acids and brain serotonin synthesis, *Brain Res.*, 488:1.

Heslop, K., Portas, C.M., and Curzon, G., 1991, Effect of altered tryptophan availability on tissue and extracellular serotonin in the rat cortex, Proc. 5th Int. Conf. In Vivo Methods, 259.

Heyes, M.P., Quearry, B.J., and Markey, S.P., 1989, Systemic endotoxin increases L-tryptophan, 5-hydroxy-indolacetic acid, 3-hydroxykynurenine and quinolinic acid content of mouse cerebral cortex, *Brain Res.*, 491: 173.

Heyes, M.P., et al., 1992, Quinolinic acid and kynurenine pathway metabolism in inflammatory and non.inflammatory neurological disease, *Brain* 115: 1249.

Hockney, R.A., Campling, G.M., Laver, D.A., Castell, L.M., Da Roza Davis, J.M., and Cowen, P.J., 1992, Biochemical stress in carers, J.Psychopharmacol., 5: Br.Assoc. Psychopharmacol/. Eur. Biol. Psychiat. Soc. Meeting, Abstracts, A16.

Holzman, D., 1993, Inflamed debate over neurotoxin, *Science*, 259: 25.

Hunsicker, K.D., Mullen, B.J., and Martin, R.J., 1992, *Physiol. Behav.*, 51: 325.

Jessy, J., Mans, A.M., DeJoseph, M.R., and Hawkins, R.A., 1990, Hyperammonaemin causes many of the changes found after portocaval shunting, *Biochem. J.*, 272: 311.

Jimerson, D.C., Wolfe, B.E., Metzer, E.D., Levine, J.M., and Cooper, T.B., 1994, Blunted neuroendocrine responses to serotonergic challenge in bulimia nervosa, *Neuropsychopharmacology*, 10:79S.

Joseph, M.S., Brewerton, T.D., Reuss, V.I., and Stebbins G.T., 1984, Plasma L-tryptophan/neutral amino acid ratio and dexamethasone suppression in depression, *Psychiatry Res.*, 11:185.

Karege, F., Widmer, J., Bovier, P., and Gaillard, J-M., 1994, Platelet serotonin and plasma tryptophan in depressed patients: effects of drug treatment and clinical outcome, *Neuropharmacology*, 10: 207.

Kaye, W.H., Gwirtsman, H.E., Brewerton, T.D., George, D.T., and Wurtman, R.T., 1988, Bingeing behaviour and plasma amino acids: a possible involvement of brain serotonin in bulimia nervosa, *Psychiat.Res*, 23: 31.

Kennett, G.A., Curzon, G., Hunt, A., and Patel, A.J., 1986, Immobilization decreases amino acid concentrations in plasma but maintains or increases them in brain, *J.Neurochem.*, 46: 208.

Knott, P.J., and Curzon, G., 1972, Free tryptophan in plasma and brain tryptophan metabolism, *Nature*, 239: 452.

Knott, P.J., Hutson, P.H., and Curzon, G., 1977, Fatty acid and tryptophan changes on disturbing groups of rats and caging them singly, *Pharmacol. Biochem. Behav.*, 7: 245.

Lambert, P.D., Wilding, J.P.H., Turton, M.D., Ghatei, M.A., and Bloom, S.R., 1994, Effect of food deprivation and streptozotocin- induced diabetes on hypothalamic neuropeptide Y release as measured by a radioimmunoassay-linked microdialysis procedure, *Brain Res.*, 656, 135.

Litman, D.A., and Correia, M.A., 1985, Elevated brain tryptophan and enhanced 5-hydroxytryptamine turnover in acute hepatic herme deficiency: clinical implications, *J.Pharmacol. Exp. Ther.*, 232: 337.

Lucca, A., Lucini, V., Piatti, E., Ronchi, P., and Smeraldi, E., 1992, Plasma tryptophan levels and plasma tryptophan/neutral amino acid ratio in patients with mood disorder, patients with obsessive-compulsive disorder, and normal subjects, *Psychiatry Res.*, 44: 85,

Maes, M., DeRuyter, M., and Suy, E., 1987, The renal excretion of xanthurenic acid following L-tryptophan loading in depressed patients, *Human Psychopharmacology*, 2: 231.

Maes, M., Claes, M., Schotte, C., Delbeke, L., Jacquemyn, Y., Verkerk, R., De Meester, I., and Scharpe, S., 1992, Disturbances in dexamethasone suppression test and lower availability of L-tryptophan and tyrosine in early puerperium and women under contraceptive *Therapy. J.Psychosomat. Res.*, 191-197.

Maes, M., Meltzer, H.Y., Scharpe, S., Bosmans, E., Suy, E., De Meester, I., Calabrese, J., and Cosyns, P., 1993, Relationships between lower plasma L-tryptophan levels and immune-inflammatory variables in depression, *Psychiatry Res.*, 49: 151.

Mathis, P., Schmitt, L., Benatia, M., Granier, F., Ghisolfi, J., and Moron, P., 1988, Perturbations des acids amines plasmatiques et depression, *L'Encephale*, 14: 77.

Menkes, D.B., Coates, D.L., and Fawcett, J.P., 1994, Acute tryptophan depletion aggravates premenstrual syndrome, *J.Affect. Dis.*, 32: 37.

Moller, S.E., Kirk, L., and Honore, P., 1979, Free and total plasma tryptophan in endogenous depression, *J.Affect. Dis.*, 1:69.

Moller, S.E., Bech, P., Bjerrum, H., Bojholm, S., Butler, B., Folker, H., Gram, L.F., Larsen, J.K., Lauritzen, L., Loldrup, D., Munk-Andersen, E., Odum, K., and Rafaelsen, O.J. 1990, Plasma ratio tryptophan/neutral amino acids in relation to clinical response to paroxetine and clomipramine in patients with major depression, *J.Affect. Dis.*, 18: 59.

Partridge, W.M., and Fierer, G., 1990, Transport of tryptophan into brain from the circulating albumin-bound pool in rats and rabbits, *J. Neurochem.*, 54: 971.

Ploog, D.W., and Pirke, K.M., 1987, Psychobiology of anorexia nervosa, *Psychol. Med.*, 17: 843.

Record, C.O., Buxton, B., Chase, R.A., Curzon, G., Murray-Lyon, I.M., and Williams, R., 1976, Plasma and brain amino acids in fulminant hepatic failure and their relationship to hepatic encephalopathy, *Eur. J. Clin.Invest.*, 6: 387.

Robinson, M.B., Heyes, M.P., Anegawa, N.J., Gorry, E., Sina Djali, E., Mellits, D., and Batshaw, M.L., 1992, Quinolinate in brain and cerebrospinal fluid in rat models of congenital hyperammonemia, *Pediatr. Res.*, 32: 483.

Russ, M.J., Ackerman, S.H., Banay-Schwartz, M., Shindledecker, R.D., and Smith, G.P., 1990, Plasma tryptophan to large neutral amino acid ratios in depressed and normal subjects, *J. Affect. Dis.*, 19: 9.

Salter, M., Hazelwood, R., Pogson, C.I., Iyer, R., Madge, D.J., Jones, H.T., Cooper, B.R., Cox, R.F., Wang, C.M., and Wiard, R.P., 1995, The effects of inhibitors of tryptophan 2,3-dioxygenase and combined inhibitors of tryptophan 2,3-dioxygenase and 5-HT reuptake in the rat, *Neuropharmacology*, 34: 217.

Sarna, G.S., Tricklebank, M.D., Kantamaneni, B.D., Hunt, A., Patel, A.J., and Curzon, G., 1982, Effect of age on variables influencing the supply of tryptophan to the brain, *J.Neurochem.*, 39: 1283.

Sarna, G.S., Kantamaneni, B.D., and Curzon G., 1985, Variables influencing the effect of a meal on brain tryptophan, *J.Neurochem.*, 44: 1575.

Schmid-Burgk, W., Kim, J.S., Lischewski, R., and Rassmann, W., 1981, Levels of total and free tryptophan in the plasma of endogenous and neurotic depressives, *Arch. Psychiat. Nervenkr.*, 231: 35.

Schwartz, D.H., Hernandez, L., and Hoebel, B.G., 1990, Tryptophan increases extracellular serotonin in the lateral hypothalamus of food-deprived rats, *Brain Res. Bull.*, 25: 803.

Smith L.P., 1907, "Life and Letters of Sir Henry Wotton", Oxford University Press, Oxford, 1: pp 485-487.

Smith, Q.R., Momma, S., Aoyagi, M., and Rapoport, S.I., 1987, Kinetics of neutral amino acid transport across the blood-brain barrier, *J.Neurochem.*, 49: 1651.

Stanley, B.G., Schwartz, D.H., Hernandez, L., Hoebel, B.G., and Leibowitz, S.F., 1989, Patterns of extracellular norepinephrine in the paraventricular hypothalamus: relationship to circadian rhythm and deprivation-induced eating behaviour, *Life Sci.*, 45: 275.

Stein, G., Milton, F., Bebbington, P., Wood, K., and Coppen, A., 1976, Relationship between mood disturbances and free and total plasma tryptophan in postmortem women, *Br. Med.J.*, 2: 457.

Sullivan, P.A., Murnaghan, D., Callaghan, N., Kantamaneni, B.D., and Curzon, G., 1978, Cerebral transmitter precursors and metabolites in advanced renal disease, *J. Neurol. Neurosurg. Psychiat.*, 41: 581.

Sullivan, P.A., Murnaghan, D., Callaghan, N., Kantamaneni, B.D., and Curzon, G., 1980, Effect of dialysis on plasma and CSF tryptophan and CSF 5-hydroxyindoleacetic acid in advanced renal disease, *J.Neurol. Neurosurg. Psychiat.*, 43: 739.

Takada, A., Grdisa, M., Diksic, M., Gjedde, A., and Yamamoto, Y.L., 1993, Rapid steady-state analysis of blood-brain transfer of L-Trp in rat, with special reference to the plasma protein binding, *Neurochem. Int.*, 23: 351.

Teff, K.L., Young, S.N., Marchand, L., and Botez, M.I., 1989, Acute effect of protein or carbohydrate breakfasts on human cerebrospinal fluid monoamine precursor and metabolite levels, *J.Neurochem.*, 52: 235.

Voog, L., and Eriksson, T., 1992, Relationship between plasma and brain large neutral amino acids (LNAAs) in rats fed diets with different compositions at different times of the day, *J.Neurochem.*, 59: 1868.

Walsh, A.E.S., Oldman, A.D., Franklin, M., Fairburn, C.G., and Cowen, P.J., 1995, Dieting decreases plasma tryptophan and increased the prolactin response to d-fenfluramine in women but not men, *J.Affect.Dis.*, 33: 89.

Wilson, W., and Marsden, C.A., 1994, The effect of treadmill running on brain serotonin (5-HT), Proc. 6th Inst.Conf. In Vivo Methods, 223-224.