Nutrients and Affective Disorders

S.E. Møller

Lundbeck A/S, Valby-Copenhagen, Denmark

Depressive disorders are among the most common diseases in humans with approximately 11% of all adults afflicted by these disorders during any one year [1]. By year 1998, major depression was ranked fourth among the ten leading causes of the global burden of disease, and is anticipated to advance to second place by 2020 [2].

In comparison to common medical illnesses such as diabetes, hypertension, etc., depression is associated with significantly greater physical limitations, more dysfunction in ability to perform one’s social and occupational role and with poorer estimation of personal health. In addition, depressive disorders have a high tendency towards recurrence, relapse and chronicity. The accumulation of high prevalence, significant disability and lifelong nature of depressive disorders results in an impact on all the national economies throughout the world and represents significant public health problems [3]. Several lines of evidence suggest that nutrients may play a contributory role to the precipitation of and recovery from depression. This paper will not discuss ‘nutraceuticals’, which cover the hybrid area between a medicine and a food.

Biology of Depression

The original serotonin and noradrenaline hypothesis of depression, dating back more than 30 years, suggested that these brain monoamine systems were directly involved and played a primary role in depression [4, 5]. Serotonin and noradrenaline are formed from the precursor amino acids tryptophan (Trp) and tyrosine (Tyr), respectively, which are derived from the food. Basic research in the subsequent decade provided partial support for the monoamine hypotheses. However, even though Trp treatment rapidly
increases brain serotonin levels, this treatment does not produce an imme-
diate rapid antidepressant response in responsive depressed patients [6, 7].
Furthermore, results of a serial of monoamine depletion experiments in human
subjects, performed by oral administration of an amino acid mixture devoid
of L-Trp, added to the likelihood that other neurobiological factors may be
involved in addition to the monoamines. Accordingly, a revised monoamine
hypothesis was formulated, i.e., that monoamines do not have a direct effect
of regulating mood, but they do have a major modulatory role on other, as yet
unidentified, neurobiological systems involved in recovery from depression [8].

Serotonin and Affective Disorders

In the early 1970s, we initiated an open study of the therapeutic effect of
Trp in drug-free, moderately to severely depressed inpatients. Prior to treat-
ment, the patients were characterized in terms of plasma amino acid profile to
identify biological variables that might associate with clinical response. Several
variables were considered including the Trp metabolite kynurenine and the
free (non-albumin bound) fraction of Trp in plasma. At the same time, Fern-
strom and co-workers’ pioneer work was published [9], showing a correlation
between the ratio in plasma of Trp to other large neutral amino acids (LNAA)
and brain Trp concentration and serotonin formation in laboratory rats. When
this variable was applied in our clinical study, a picture emerged. Responders
to Trp treatment showed a low pretreatment plasma Trp/LNAA relative to
healthy volunteers, whereas nonresponders showed a normal ratio [6]. The
relationship between basal plasma Trp/LNAA and clinical response to L-Trp
was confirmed in a subsequent controlled study including larger samples of
depressed inpatients and healthy volunteers [7].

The association between pretreatment plasma amino acid profiles and
clinical response to antidepressant pharmacotherapy has been emphasized in
a serial of controlled clinical studies. Generally, the antidepressant effect
of serotonin-potentiating treatments, such as amitriptyline and selective
serotonin reuptake inhibitors (SSRIs), associated inversely with the plasma
Trp/LNAA, whereas the efficacy of nortriptyline, a noradrenaline-potentiating
agent, associated inversely with the plasma Tyr/LNAA [10]. The relationship
between plasma ratios Trp and Tyr to other LNAA and therapeutic response
in depressed patients to a variety of antidepressant treatments has been
confirmed by other groups [11–13].

The impact of the LNAA on brain serotonin function has been substan-
tiated in a serial of studies, in which acute depletion of Trp is produced by
administration of a 100-gram Trp-free amino acid mixture suspended in water.
In healthy volunteers, an acute Trp depletion results in a marked decrease
of cerebrospinal fluid (CSF) Trp level and a modest decrease of the sero-
tonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) level in the CSF [14].
In recently remitted depressed patients, acute Trp depletion led to a clinically significant return of depressive symptoms in the patients in whom remission was maintained with serotonin-potentiating treatment. The symptom complex and depressive cognitive content induced by the Trp depletion often closely resembled the unique clinical features manifested by the patient before successful treatment. Control testing with a balanced Trp-containing amino acid mixture produced no significant depressive symptoms [15].

Major depressive disorder with seasonal pattern, or seasonal affective disorder (SAD), or ‘winter depression’, is a variant of major depression with atypical features such as hypersomnia and increased appetite, particularly with a preference for carbohydrates, rather than the terminal insomnia and diminished appetite, which are prominent symptoms of major depression. Acute Trp depletion was found to reverse the antidepressant effect of bright light therapy in patients with SAD [16]. Furthermore, preliminary findings indicate that those patients who develop depressive symptoms during Trp depletion when they are fully remitted and off therapy remain at high risk to experience a depressive episode of SAD also in the subsequent winter [17]. Besides bright light, patients with SAD benefit, in general, from treatments with serotonin-potentiating drugs, which further emphasize the role of serotonin in the pathophysiology of SAD. Ingestion of carbohydrates increases the plasma Trp/LNAA in man and animal, and the serotonin synthesis in the rat brain. Based on these findings, it has been suggested that the excessive carbohydrate intake by patients with SAD reflects a self-medication that temporarily relieves the vegetative symptoms via an increased central serotonergic activity [18].

Bulimia nervosa is an eating disorder characterized by recurrent episodes of binge eating accompanied by extreme weight control behaviour. Reduced central serotonergic activity may contribute to the pathogenesis, since treatment with SSRIs provides symptomatic relief. Acute Trp depletion caused an increase of caloric intake and mood irritability in females with bulimia nervosa [19], and increases in ratings of body image concern and subjective loss of control of eating in females with a history of bulimia nervosa [20].

Whilst the above studies included patients suffering from a variety of affective disorders or being in remission, a further study elucidated the effect of Trp depletion in genetically vulnerable subjects. Individuals with no prior depressive episodes but with a multigenerational family history of major affective disorder showed a greater reduction in mood after acute Trp depletion than subjects without such a family history [21].

**Noradrenaline and Affective Disorders**

The role of brain noradrenaline in depression was elucidated by the noradrenaline synthesis inhibitor α-methylparatyrosine (AMPT) as a depletion tool. Administration of AMPT to depressed patients in remission on
antidepressant treatment led to a clinically significant return of depressive symptoms in patients whose remissions were maintained with noradrenaline reuptake inhibitors, but not in patients whose remissions were maintained with SSRIs. As with the Trp depletion, the symptom complex and depressive cognitive content induced by AMPT often closely resembled the unique features manifested by the patient before successful treatment [22]. There is suggestive evidence that noradrenaline depletion might also have been produced by the administration of a phenylalanine and Tyr free amino acid mixture. This treatment caused a reduction in serum Tyr/LNAA, and brain Tyr levels and hydroxylation rate in the rat [23], and a decrease of the plasma phenylalanine and Tyr levels along with a decrease of systolic and diastolic arterial pressure in healthy subjects [24].

**Nutriokinetic Studies in Affective Disorders**

The clinical and biochemical effects observed in the studies of L-Trp and the depletion studies suggest that constituents of normal daily diet can provide symptomatic relief in depressives (i.e., L-Trp) or precipitate depressive symptoms in vulnerable subjects (i.e., the LNAA), when acutely administered in pharmacological doses. A more physiological approach would be nutriokinetic studies to clarify whether some vulnerable subjects might show a disturbance of metabolism of key nutrients. A deranged metabolism resulting in a reduced availability of precursor amino acids to the brain might possibly on a long-term basis adversely affect the regulation of mood, impulsivity or aggression in susceptible subjects. To study the metabolism of proteins we applied the oral bovine albumin load test and showed a dose-dependent decrease of plasma Trp/LNAA and increase of plasma Tyr/LNAA in healthy subjects [25].

The albumin load test has been applied to patients with affective disorders. A dose of 12.5 g albumin dissolved in 200 ml water was administered to a female patient, Ms. A, who had suffered from bipolar I disorder for 19 years and had had more than 20 psychiatric hospitalizations. Ms. A was euthymic (neither depressed, nor manic) and free of medication for 4 days prior to the albumin load test. Following the albumin ingestion, the plasma Trp/LNAA decreased similarly in Ms. A and age-matched female healthy controls. However, the slope of Ms. A’s plasma Trp/LNAA curve from 1 to 4 h was significantly smaller than that of the controls ($p < 0.001$; Fig. 1). Two days later, Ms. A showed clear depressive symptoms, and treatment with an SSRI was initiated. After 5 weeks the SSRI was discontinued due to treatment failure. Ms. A was psychotic and severely depressed when the second albumin load test was performed, following 4 drug-free days. Again, the slope of Ms. A’s plasma Trp/LNAA curve from 1 to 4 h differed significantly from the control curve ($p < 0.001$; Fig. 1), but not from the slope observed in the first load test.
Fig. 1. Variation with time of the plasma Trp/LNAA (left) and Tyr/LNAA (right) in 6 healthy female controls (▲), with mean age 28 (range 23–28), and in a 37-year-old female bipolar depressed patient (Ms. A) in euthymic state (●), in depressive state (○), and in remission on L-Trp plus lithium (■) after ingestion of 12.5 g albumin dissolved in 200 ml water at 0 h. Control results are presented as the mean ± 1 SD. The slope of the Trp/LNAA curves in euthymic and depressive state differed significantly from that of the controls (p < 0.001) [from 26, with permission from the publisher].

Following successful treatment with L-Trp plus lithium, a third albumin load test was performed. This time, Ms. A’s plasma Trp/LNAA curve tended to show curvilinear shape with slightly elevated levels at 1.5 and 2 h compared with the controls (Fig. 1). The failure of Ms. A to normalize the plasma Trp/LNAA curve in the first two albumin load tests suggests a reduced Trp transport to the brain and, in turn, a decreased brain serotonin formation following protein consumption. Even though Ms. A was in a clinically neutral state during the first load test, she may have been biochemically predisposed to the psychosis, which became evident 2 days after the load test [26].
Nutrients and Affective Disorders

Fig. 2. Variation with time of the plasma Trp/LNAA (left) and Tyr/LNAA (right) in 6 healthy female controls (▲), with mean age 28 (range 23–38), and in 2 aggressive female patients, Ms. B, aged 48 (●), and Ms. C, aged 61 (○), after ingestion of 12.5 g albumin dissolved in 200 ml water at 0 h. Control results are presented as the mean ± 1 SD. The slope of the patients' Trp/LNAA curves from 1 to 4 h differed significantly from that of the controls (p < 0.005, or less) [from 26, with permission from the publisher].

Central serotonin and noradrenaline pathways take part in the regulation of behavioural impulsivity and aggression. The albumin load test was also performed in 2 female schizophrenic patients with marked aggressive and impulsive behaviour. Initially, the plasma Trp/LNAA decreased in the 2 patients similarly to the controls. However, the slope of the patients’ Trp/LNAA curves from 1 to 4 h was significantly smaller than that of the controls (p < 0.005 or less; Fig. 2). Furthermore, plasma Tyr/LNAA was increased above mean + 2 SDs of the controls from 3.5 to 4 h in the 1 patient, and from 0 to 4 hours in the other patient. The decreased availability of Trp and increased availability of Tyr to the brain following protein ingestion may possibly affect brain serotonin and noradrenaline function adversely in susceptible subjects [26].

Oral Contraceptives and Affective Disorders

One of the recognized adverse reactions to combined oral contraceptives (OC), i.e., oestrogen-progestogen preparations, is depression, and a
deranged precursor amino acid availability to the brain may likely play a role in precipitating and sustaining the depressive symptoms. OC users have shown significantly decreased plasma Tyr/LNAA at the mid-cycle and luteal phases compared to the levels in females not taking OC. Moreover, the peak level of plasma Tyr/LNAA following an albumin load test in OC users did even not reach the basal level observed in the controls (Fig. 3), suggesting that Tyr supplementation in the form of proteins may not compensate for the decreased Tyr availability to the brain [27]. The decreased plasma Tyr level in OC users was associated with a significantly increased activity of the liver enzyme tyrosine transaminase [27]. The reduced Tyr transport to the brain in OC users may result in a substrate-limited decrease of brain noradrenaline formation, which secondarily may contribute to disturbances of noradrenaline-regulated functions, e.g., mood, coping with stress, appetite, food preferences, and blood pressure in susceptible subjects. There are indications that a surplus of calories ingested by OC users in comparison to control subjects almost exclusively is accounted for by carbohydrates, rather than proteins, which may further tend to aggravate the induced Tyr deficit [28].

A further nutritional aspect of OC use is derived from the competition between the oestrogen conjugates and pyridoxal phosphate. The enzyme
aromatic amino acid decarboxylase is pyridoxal phosphate-dependent and may, therefore, be sensitive to competitive action from the oestrogen conjugates. Although some OC users consuming diets of poor quality may possibly develop a true pyridoxal phosphate deficiency, there is a general agreement that most OC users do not show an absolute deficiency of pyridoxal phosphate. However, a functional deficiency is likely to occur, which may cause a decreased formation of serotonin and noradrenaline and add to the disturbances caused by a decreased Tyr availability [for discussion and references, see 29].

Aspartame and Affective Disorders

Many food products contain the artificial sweetener aspartame, which is hydrolysed after oral ingestion in the gastrointestinal tract resulting in the release of aspartate and phenylalanine (Phe) into the bloodstream, from where Phe enters the brain in competition with the other LNAA. We anticipated that Phe derived from aspartame might possibly be metabolized differently from Phe derived from food, and that this difference secondarily could affect brain function in vulnerable subjects. Healthy volunteers received orally 0.56 g Phe in the form of 1.0 g aspartame or 12.2 g albumin dissolved in 200 ml water, or water alone. The area under the curve for plasma Phe was 40% greater, albeit not significantly so, after aspartame compared with albumin intake. The increased clearance rate of Phe after albumin relative to aspartame may be caused by the significant increase of insulin, on which aspartame had no effect. The plasma Phe/LNAA decreased slightly in response to albumin, but increased significantly \( (p < 0.01) \) by 55% after aspartame intake and remained significantly increased for 2 h (Fig. 4). Plasma Tyr/LNAA increased and plasma Trp/LNAA decreased modestly after aspartame intake. Since Phe is a very strong competitor of LNAA transport to the brain, the results suggest that the persistent increase of availability of Phe to the brain following intake of products containing aspartame, rather than the slight decrease after protein consumption, may adversely affect subjects susceptible to affective reactions [30].

This hypothesis gained support from a cross-over study in which aspartame 30 mg/kg per day or placebo was administered double-blind for 7 days to depressed patients in remission in comparison to control subjects. The study was halted prematurely by the Institutional Review Board after a total of only 13 subjects had completed the study because of severity of the reactions within the group of patients with a history of depression. Despite the small number of subjects who completed the study, there was a significant difference between aspartame and placebo in the number and severity of symptoms for patients with a history of depression, whereas for individuals without such a history there was not [31]. The study concluded that individuals with mood disorders
Nutrients and Affective Disorders

Fig. 4. Variation with time in percentage of basal levels of plasma Tyr/LNAA, Phe/LNAA, and Trp/LNAA in 6 healthy male subjects after ingestion of 200 ml water alone (control; ○), with 1.0 g aspartame (●), or 12.2 g albumin (■) at 0 h. Results are presented as the mean ± 1 SEM. p < * 0.05; **0.01 in comparison with control levels [from 30, with permission from the publisher].

are particularly sensitive to aspartame, and its use in this population should be discouraged.

Brain Monoamines and Food Selection

Basic studies suggest that intake of proteins and carbohydrates, and in particular the proportion between these macronutrients in the diet, is regulated in part by brain serotonin and noradrenaline. There is also evidence that consumption of a carbohydrate meal increases the plasma Trp/LNAA in animal and man, and a protein meal decreases the plasma Trp/LNAA and increases the plasma Tyr/LNAA in animal and man. These effects may secondarily cause parallel changes of brain serotonin and noradrenaline [see 28 for references]. We were interested in studying the suggested interaction between food selection and brain monoamines in healthy volunteers. In a preliminary study, there was a significant association between the sum of the plasma Trp/LNAA and Tyr/LNAA in fasting female subjects and the choice of between-meal snacks as reported on a questionnaire. Females with a sum of the two ratios above the mean preferred snacks with a high proportion of carbohydrate to proteins to snacks with relatively low proportions, as compared with subjects with a sum of plasma ratios below the mean [32].
In a subsequent controlled study, the plasma Trp/LNAA and Tyr/LNAA were determined in 31 fasting healthy female subjects who were subsequently allowed to compose individual breakfast meals from a buffet selection of 25 different dietary products. The proportion of carbohydrate to protein eaten was significantly and directly correlated with the sum of plasma Trp/LNAA and Tyr/LNAA ($r = 0.50; p < 0.005$, Fig. 5), thus confirming the preliminary study. In addition, the specified meal composition was directly correlated with age ($r = 0.42; p < 0.02$, Fig. 5), and these two independent variables associated with 37% of the variance of the proportion of carbohydrate to protein consumed ($F[2, 28] = 8.40; p < 0.005$) [28].

Additional blood samples were collected from the volunteers at 2 h after the meal. Subjects who consumed meals with a proportion of carbohydrates to proteins below the mean of the full sample showed an increase of plasma Tyr/LNAA and a decrease of Trp/LNAA, whereas subjects who consumed meals with a high proportion of carbohydrates to proteins showed an increase of plasma Trp/LNAA [28] (Fig. 6).

The results suggest a relationship between brain serotonin and norepinephrine, reflected in the plasma Trp/LNAA and Tyr/LNAA, and the proportion of carbohydrate to protein consumed by humans, however, it is difficult to dissociate cause and effect.

Logically, individuals would be expected to select meals with a proportion of carbohydrates to proteins, which after consumption would change the plasma Trp/LNAA in direction of the population mean. On the contrary, individuals with plasma Trp/LNAA below the population mean composed and consumed meals that further decreased the plasma Trp/LNAA, and individuals...
Amino Acids and Personality Features

The association between plasma amino acid profiles and 5-HIAA level in the CSF, on the one side, and aggression and personality features, on the other side, was studied in 52 individuals who were hospitalized due to a suspected slipped disc, but who were otherwise normal and in good health. None of the subjects had ever experienced an episode of psychiatric disease. Some of the CSF collected at the neurological investigation was used for the determination of amino acids and monoamine metabolites. Blood samples for the determination of plasma amino acids were collected within an interval of 1 h from the
lumbar puncture. CSF and blood samples were collected from fasting subjects, who furthermore completed a questionnaire developed for the assessment of nonpathological aggression. There was a significantly positive correlation between CSF 5-HIAA and extroverted aggression \((r = 0.38; p < 0.01)\), and a significantly negative correlation between CSF 5-HIAA and introverted aggression \((r = -0.31; p < 0.05)\). In addition, males \((n = 25)\) showed a significantly positive correlation between extroverted aggression and plasma Trp and Trp/LNAA \((r = 0.47\) and \(0.45\), respectively; \(p < 0.05)\) [33]. These results lend support to the idea that components of normal diet, \textit{i.e.} carbohydrates and proteins, \textit{via} effects on plasma amino acid profiles, may have impact on personality characteristics, more specifically on traits of aggression.

### Nutrient-Derived Substances and Affective Disorders

A number of nutrient-derived substances may play a role in affective disorders, although this is far less substantiated than the macronutrients, which cause a major impact on the brain monoaminergic systems. In a preliminary placebo-controlled study, large doses \((9.6\text{ g/day})\) of n-3 fatty acids increased the length of remission in patients with bipolar disorder (manic-depressive illness) compared with those given an olive-oil placebo [34]. Another aspect comes from the possible role that folate is thought to play in mood regulation. A study comprising more than 200 outpatients with major depressive disorder showed that subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to treatment with an SSRI [35]. For several years, the possible role of decreased serum cholesterol has been subject for discussion in relation to aggression, depression and suicidal behaviour. The association between low cholesterol and death from suicide still remains obscure. A large-scale prevention study showed an association between low serum total cholesterol at baseline and a heightened risk of major depressive disorder and death from suicide [36].

### Conclusion

Evidence has been presented that nutrients may play a contributory role to the precipitation of affective reactions including depression in susceptible subjects. These effects associate with changes of plasma amino acid profiles, which likely cause alterations of brain monoaminergic function. In addition, use of OC or intake of aspartame, which also change the plasma amino acid pattern adversely, are reported to provoke affective reactions in these subjects.

Acute intake of proteins or carbohydrates by healthy subjects brings about changes of the plasma amino acid profile, which, conceivably, causes parallel...
changes of brain monoamine levels. It is hypothesised that long-term metabolic effects of diet in some subjects may contribute to sustaining or accentuating personality features, which in part are related to brain monoaminergic function, such as mood, pain sensitivity and aggressive behaviour.

References

34. Stoll AL, Severus WE, Freeman MP et al. n-3 fatty acids in bipolar disorder. Arch Gen Psychiatry 1999; 56: 407–12.

Discussion

*Dr. Fernstrom:* Aspartame is a dipeptide that contains aspartate (aspartic acid) and phenylalanine. The reason phenylalanine goes up is because of the phenylalanine in the dipeptide. In the Walton study [1], just to point out the obvious, they were using 30 mg/kg/day, which for a 70-kg person would be 2 g aspartame/day. That's 200 times sweeter than sugar, so no-one would ever eat that amount. In follow-up studies since aspartame was released in 1983, people have consumed at most about 3 mg/kg per day. So 2 g is a very high dose, and not surprisingly you see large increases in phenylalanine.

My second point is that you didn’t mention in your study on aspartame whether there was any Hamilton effect or behavioral effect. Finally, in the study with the albumin, where I was intrigued by the increase in tyrosine ratios, did you measure any
Nutrients and Affective Disorders

Hamilton depression rating changes? It would be interesting to know that, because the tyrosine ratio was going up and the tryptophan ratio going down.

**Dr. Møller:** The aspartame study was performed in healthy volunteers and we gave only half the dose given in the Walton study – that is, 0.57 g of phenylalanine, which is equivalent to 1 g aspartame, so a rather moderate dose. There was absolutely no effect in terms of behavioral change in our subjects, and no subjective effects of any kind. We had not expected any, as these were healthy young men. In relation to the tyrosine ratios and the albumin test, this was also initially performed in healthy volunteers. Again, even though there was a significant decrease in the tryptophan ratio, there were no subjective feelings or mood change. Healthy people probably have a barrier or are not susceptible to such changes. Young now says that the initial group he investigated, in whom there appeared to be mood change, may not have been an ideal group of healthy subjects. I think the consensus now is that when you give this amino acid mixture without tryptophan to healthy volunteers, you will see no changes apart from a bad taste sensation. Also, if you give this amino acid mixture without tryptophan to patients with moderate or severe depression, you might expect the depression to be aggravated, but it isn’t. The Hamilton score does not change, and this is difficult to explain. In fact, you may see a slight improvement after 1 or 2 days in these depressed patients, though this does not persist. But there was no aggravation of the depression following tryptophan depletion and that’s difficult to explain.

**Dr. Fernstrom:** To follow that point up, I look at amino acids as constituents of the diet, not as drugs. When we use the tryptophan depletion paradigm we are almost in the realm of drug use: 100 g of free amino acids is quite a load. Nonetheless, they are still amino acids and not tricyclic antidepressants or serotonin reuptake inhibitors, so I have always imagined that to tease out an effect of a dietary constituent you have to be fairly clever in how you design the experiment; thus seeing tryptophan depletion work in a remitted depressed patient but not in a normal person or in someone who is already seriously depressed makes perfect sense to me. An analogy might be that if you gave an additional dose of an antidepressant to someone who was already depressed and being treated, you wouldn’t necessarily see an improvement. I don’t think the body is designed to have major mood swings in response to eating carbohydrate or protein, or to having a rise or fall in tryptophan in the physiological range. That would be counterproductive I think.

**Dr. Møller:** I agree.

**Dr. Fernstrom:** One other thing: there are studies by Simon Young where he claims that when CSF is sampled from human patients after they’ve had a carbohydrate or protein load, the CSF tryptophan doesn’t change. This contrasts with the comments you make. In fact, his findings are at variance with much of the other data. I wonder what you think about that? What I didn’t show in my talk was that if you feed a rat a meal of protein and then 2 hours later feed a meal of carbohydrate, there is no increase in brain tryptophan; it’s simply asking too much metabolically when an animal is already replete with food for carbohydrate to raise tryptophan and serotonin. So over the 24-hour period, can you really expect that people will continue to select carbohydrate versus protein on the basis of the perceived changes in the tryptophan/serotonin ratio?

**Dr. Møller:** First, the effects on the CSF. It’s true that the effects on tryptophan and 5-HIAA can be subtle in the CSF following a tryptophan depletion test, but recently Williams and his group reported that they had given this amino acid meal to healthy volunteers and they did show a significant decrease of tryptophan in the CSF and also of 5-HIAA, although the decrease in 5-HIAA was not substantial [2] So I think that on balance, although there are not many of these kinds of studies, there is an effect of the tryptophan depletion test on tryptophan and 5-HIAA in the CSF in the expected direction.
The second question you raised was the long-term effect. I deliberately arranged for the subjects to be fasted for at least 12 hours, because otherwise there could have been a lot of confounders. So what happens afterwards? We should maybe have asked the subjects about the composition of their meals over the following day to analyze the situation further, but it was too complicated to do that at that time. However, it would certainly have been necessary in order to elucidate the whole mechanism.

Dr. Langhans: How exactly does light, or the lack of light, affect brain serotonin?

Dr. Møller: Serotonin in the brain has, of course, not been measured in life. The results I showed were postmortem measurements. Carlsson and his group [3] have hypothesized that light could influence these measurements, but as far as I know, this hypothesis has not been pursued.

Dr. Holm: I am wondering about the mechanisms behind the effects of carbohydrates on the plasma levels of tryptophan. Did you measure insulin for instance? One could envisage the possibility that carbohydrate increases insulin production, leading to reduced fatty acids, and then to a reduction in tryptophan metabolism, so the total amount of tryptophan should be increased. The main determinant of the entry of tryptophan into the brain is not free tryptophan but the binding of tryptophan to albumin; thus total tryptophan is more important than free tryptophan. Can you comment on the possible role of insulin and free fatty acids on both the plasma levels of tryptophan and its entry into the brain?

Dr. Møller: It has been an issue for many many years about whether free tryptophan only or total tryptophan can gain access to the brain. There have been hypotheses that tryptophan is too firmly bound to albumin for it to enter the brain, while others claim that the tryptophan bound to albumin is stripped off when it passed the blood-brain barrier because the affinity of tryptophan for the blood-brain barrier is greater than for albumin, so the important variable is in fact total tryptophan. We have tried to include free tryptophan instead of total tryptophan in the plasma ratio in our studies of depression but the results didn’t make sense, so we now always used total tryptophan. With total tryptophan there is a substantial correlation with the clinical effects of a large variety of antidepressants. We have studied 9 or 10 different treatments for depression, and practically all the studies have shown an association with a ratio that includes total tryptophan [4].

The question of insulin is a very interesting and relevant one, because you may recall that many years ago large doses of insulin were given as a way of treating depression. Nobody really knew how it worked at that time, though clinicians found that it worked. Maybe the effect was explained by hypoglycemic convulsions, but it could also be that insulin changed the ratio of tryptophan to the large neutral amino acids in the plasma, because what insulin does is to promote the transport of the other large neutral amino acids into tissues, where they are built into proteins, whereas tryptophan is transferred into tissues to a much lesser extent. This causes an increase in the tryptophan ratio and improved transport of tryptophan into the brain. So insulin is very important.

Dr. Fernstrom: The issue of albumin, free fatty acids, tryptophan, and transport into brain has been around for 30 years now. The initial studies reported in the 1970s claimed that the transport of tryptophan into the brain was highly dependent on how tightly it was bound to albumin in the blood. Tryptophan is the only amino acid that binds appreciably to a serum protein – around 80% is bound to albumin, depending on the species. From a pharmacologic perspective, bound drug, or in this case bound amino acid, has no bioavailability. So the idea was that the factor controlling the access of tryptophan to the brain was the percentage of binding to albumin. If you massively unbind tryptophan from albumin you should see a big change in tryptophan uptake in the brain. Indeed, using drugs that unbind tryptophan from albumin, one did in fact see that effect. But there are other physiological variables – for example
tryptophan binds to albumin, but free fatty acids also bind to albumin, and you can unbind tryptophan from albumin by increasing the blood free fatty acid level. The binding is thus competitive. A series of studies followed showing that if dietary fat was used to modulate blood fatty acids, the binding and unbinding of tryptophan had nothing to do with tryptophan transport. A few years later, Partridge explained this by showing that the affinity of tryptophan for the transport carrier in the blood-brain barrier is much greater than it is for albumin, so as an albumin molecule slips through a brain capillary with tryptophan associated with it, the tryptophan is stripped off the albumin. Subsequent studies showed that you could cause huge variations in free tryptophan levels in blood and find no change in the brain, and yet in the 1990s this idea persisted. We did a study that was published some years ago in which we held everything constant except the free fatty acid level and the free tryptophan level, and even with gross manipulation of those two variables we were unable to show any connection between the percentage of free tryptophan and the amount that ultimately got into brain. So I think this idea has been beaten into the ground and yet it persists. Physiologically you really see no relation between tryptophan binding in blood and its transport into brain.

**Dr. Rosenberg:** In relation to possible genetic differences in the response to amino acid loads, could you just dwell for a moment on the mechanism? If I remember correctly, there was a difference between subjects who had a family history of depression and those without such a history with respect to the depressant effects of amino acids loads with or without tryptophan. Where do you suspect the differences lie? Are there differences in the neutral amino acid transport system in the intestine between those two groups? Or are there differences in the disposal of amino acids and or how easily they cross the blood-brain barrier? What other differences can one observe between those two groups in the handling of those amino acid loads?

**Dr. Møller:** This is very difficult to answer because it’s purely guesswork. There is no difference between depressed patients and controls in amino acid handling during the period of loading, so it is not a quantitative effect. I think the effect is more likely to be a related to the serotonergic neurons in the brain and the extent to which they do or do not function normally. At present there is no answer to why people get depressed or what is the mechanism of recovery. However, amino acid depletion studies give some clues to understanding where the problem may lie. The current view is that the disease is associated with changes in the presynaptic neurons, not in the receptors. It may be that the function of the serotonergic neuron per se is abnormal, and it may become abnormal in susceptible subjects under the influence of some minor environmental factor.

**Dr. Langhans:** Did the age effect that you showed in carbohydrate and protein selection reflect a continuous distribution across the whole age range or was there a cut-off point?

**Dr. Møller:** It was a continuous linear association.

**Dr. Uauy:** What about nutrients that may modify the blood-brain barrier, for example n-3 fatty acids? There is both epidemiological data and some preliminary clinical trials. Is there a relation between fish oil consumption and decreased depression?

**Dr. Møller:** This has not been investigated very much. A study was done in which unsaturated fatty acids were given to patients with bipolar disorder to assess whether they had any influence on time to remission [5]. It appeared that patients who took PUFA did better than the those who did not, but I would like to see the results replicated before I accept this as a significant finding.

**Dr. Payette:** I understood that your study population was mainly young adults, while depression is more prevalent in the elderly. Do you think the same associations
between tryptophan and mood are likely to be present in elderly people as in young adults?

Dr. Møller: There is a slight decrease in the tryptophan ratio with age, so you could anticipate that this might contribute to a higher prevalence of depression in the elderly, but it is so slight that I would not like to suggest that it has much practical significance. I think it is much more likely that depression in elderly people is related to social or nutritional factors; there could be many environmental factors contributing to depression in the elderly.

References