A Precursor Study of the Indoleamine and Catecholamine Hypotheses of Depression Using the Dietary Tryptophan and Tyrosine Ratios

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Abstract

The indoleamine and catecholamine hypotheses of depression were tested by studying the tryptophan and tyrosine ratios of 16 women in a representative sample of the Swedish population, who were 46, 50, or 54 years old. The two ratios were estimated from the mean daily intake of six large neutral amino acids from the diet. Depression was not associated with low tryptophan ratios, but a significant association was found between low tyrosine ratios and depression among 54 year olds and among women without menstruation. Tyrosine ratios were not associated with the seasonal differences, and carbohydrate intake and the carbohydrate/protein ratio were not associated with depression.

Key Words

Indoleamine hypothesis of depression, catecholamine hypothesis of depression, tryptophan ratio, tyrosine ratio, depression, seasonal differences, carbohydrate, large neutral amino acids, menopause, carbohydrate/protein ratio.

Introduction

There are currently two widely held biochemical hypotheses on depression. The indoleamine (IA) hypothesis suggests that deficient transmission of serotonin (5-HT) leads to depression (Shopsin and Feiner, 1984), while the catecholamine (CA) hypothesis emphasizes the importance of another neurotransmitter nore-pinephrine (NE) in the biochemistry of the neurons (Schildkraut, 1965).

Since both 5-HT and NE are derived from amino acid precursors in the serum, namely, tryptophan (TRP) and tyrosine (TYR) respectively, one reasonable way to test these hypotheses is to take the so-called precursor-load strategy. In this approach, patients are treated with either L-TRP or L-TYR, depending on the hypothesis to be tested.

In order to study the effect of TRP or TYR in a precursor study, it is necessary to take the ratio between TRP or TYR and the competing large neutral amino acids (LNAA) in the serum into account (Pard-ridge, 1977; Fernstrom and Wurtman, 1972; Fernstrom and Faller, 1978). However, despite the importance of the TRP ratio, as van Praag (1984) points out, there are only a small number of studies which have taken this ratio into account, and this may explain some of the confusing results of precursor studies using TRP. There are even less studies with L-TYR as a precursor of NE, taking the TYR ratio into account.

Yet another problem in studies of amino acid precursors deals with diet. Since TRP and TYR as well as the other LNAA are derived from diet, it is desirable to look at the total intake of all LNAA from the diet. The purpose of this study, then, is to test (1) the IA hypothesis by examining the TRP ratio, and (2) the CA hypothesis by examining the TYR ratio. Both ratios are to be calculated from the intake olamino acids from the diet. The two ratios can then be examined in terms of the presence or absence of depression.

Method

In order to test the two hypotheses, the data of the "women in Gothenburg" project (Bengtsson et al, 1973) were reanalyzed. This project began in 1968, and a representative sample of women in the city of

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Gothenburg, Sweden, who in January, 1968 were 38, 46, 50, 54, or 60 years old were studied. They underwent gynacological, dental, hematological and other examinations. Some of them also participated in dietary and psychiatric studies, and in all, 286 women of 46, 50, or 54 years old were in both studies.

Their psychiatric state in 1968 or 1969 was studied by the Hamilton Rating Scale (Hamilton, 1967) and other psychiatric data were later reclassified in terms of the DSM-III criteria (American Psychiatric Association, 1980). This was a point prevalence study of past two weeks, and it took one year to complete (Hallstrom, 1984). In all, there were 16 participants who had experienced endogenic depression in terms of the DSM-III criteria, and their Hamilton Rating Scale scores ranged from 5 to 30, the mean being 16.75. The age distribution of the 16 women was as follows: 46 years old (N = 3), 50 years old (N = 4), and 54 years old (N = 9).

For the control group, 16 women without depression during past two weeks in terms of both the Hamilton Rating Scale and the DSM-III criteria were chosen. They were selected by means of a systematic sampling in the corresponding three age groups and also proportionally to each age group. This means there were 18 control and depressed 54 year old women, making up more than 56% of the sample. The information on the dietary habits of the 32 women in the present sample was obtained by reanalyzing the detailed interview by a dietitian as well as a questionnaire from 1968 or 1969. In the original design of the "women in Gothenburg" project, the information on dietary habits thus obtained was at the same time checked against the mean 24-hour urinary nitrogen excretion. The protein intake estimated from urinary nitrogen was reported to deviate insignificantly in terms of the statistics from the interview and questionnaire data (Lenner et al, 1977).

In order to obtain the dietary TRP or TYR ratio for each subject, the mean intake of each amino acid per day was estimated from the information on the diet. The amount of amino acids for each food item was estimated by referring to the nutritional tables prepared by the Swedish National Food Administration (Statens Livsmedelverk, 1986). The total amount ' of each amino acid was then divided by its formula weight, and the resulting figures were used for calculating the two ratios by using the following formula: the dietary TRP ratio = TRP / (TYR + PHE + LEU + ILE + VAL); and the dietary TYR ratio = TYR / (TRP + PHE + LEU + ILE + VAL).

Results

For the testing of the IA hypothesis, the relationship between the dietary TRP ratio and the presence or absence of depression was examined. The difference between the mean dietary TRP ratio for the control group (X = .029 274; s.d. = .000 447; N = 16) and the experimental group (X = .029 229; s.d. = .000 547; N = 16) was insignificant at the one-tailed 5% level (Mann-Whitney's U = 124; N = 32; n.s.). Since the sample consisted of three age groups, three additional tests were conducted for each age group. The results show no statistical significance for the 46 year olds ($p = .350$; N = 6; n.s.), 50 year olds ($p = .343$; N = 8; n.s.), and 54 year olds (U = 37; N = 18, n.s.) by the one-tailed Mann-Whitney U test (see Table 1).

Since it is known that carbohydrate meals raise the serum TRP ratio (Fern-strom, 1981), the carbohydrate intake from the diet was also studied. The control group consumed more carbohydrates (X = 220.99 g; s.d. = 45.21; N = 16) than the experimental group (X = 208.71 g; s.d. = 59.40; N = 16), but this is insignificant at the 5% level (t = .637; d.f. = 30; N = 32; n.s., one-tailed). Three additional tests for the three age groups showed no significant difference either ($p = .350$; N = 6;$p = .171$; N = 8; $p > .05$; N = 18; one-tailed Mann-Whitney's test).

In the case of testing the CA hypothesis, the relationship between the dietary TYR ratio and depression was examined. The ratio for the control group was significantly higher (X = .106 817; s.d. = .004 636; N = 16) than the ratio for the experimental group (X = .103 747; s.d. =002949; N = 16), in terms of both the t test of unequal variance (t = 2.227; d.f. = 30; N = 32; $p < .025$, one-tailed) and the Mann-Whitney U test (U = 75; $p = .025$; N = 32; one-tailed). This suggests that a lower TYR ratio is associated with a tendency for depression.

Three tests were also conducted for the three age groups separately. Although there was no significant relations for the 46 year olds (U = 5; p = .650; N = 6, n.s.) and for the 50 year olds (U = 10; p < .557; N = 8, n.s.), a significant relationship was found for the 54 year olds (U = 15; p < .025; one-tailed; N = 18). This means the significant relationship between the low TYR ratio and depression is due to the significant relationship among the 54 year olds. This suggests the possible relevance of menopause. For this reason, the sample was divided into two groups in terms of presence or absence of menstruation. Among those without menstruation, the TYR ratio for the control group (X = .107 761**;** N = 8) was significantly higher than the ratio for the experimental group (X = .103 212; N = 8) by the Mann-Whitney U test (U = 13; p = .025; one-tailed). However, no difference was found among those with menstruation (U = 26; p = .433; one-tailed; N = 15).

Since it is known that cold increases the brain turnover rate for NE and makes the neurons sensitive to TYR (Gibson and Wurtman, 1973), the 16 subjects in the experimental group were divided into two subgroups on the basis of when they were studied. There were ten subjects who were interviewed some time between April and September, and six subjects were interviewed between October and March. However, there was no statistical difference between these two groups in regard to the TYR ratio (U = 28; N = 16; n.s.; Mann-Whitney U test, one-tailed).

Since a significant relationship between low TYR ratios and depression was found only among the 54 year olds, the same test was repeated for the nine subjects in this age group. The four subjects in the April-September subgroup and the five subjects in the October-March subgroup did not show any significant difference (U = 8; p = .365; n.s., Mann-Whitney U test, one-tailed). Among the depressed women without menstruation, the April-September subgroup (N = 4) and the October-March subgroup (N = 4) showed no significant difference either (U = 7; p = .443; n.s., Mann-Whitney test, one-tailed). This suggests that seasonal difference is not significant enough to be taken into account in considering the TYR ratio and consequently depression.

It is known that, as in the case of TRP, a carbohydrate meal raises the serum TYR ratio (Fernstrom and Faller, 1978; Gibson and Wurtman, 1978), but more carbohydrate intake from the diet is not associated with less depression, as reported above in testing the IA hypothesis. An additional factor to be examined in this context is the relative intake of protein compared with carbohydrates. It is reported that in the rat, short-term appetite for carbohydrate and protein is associated with the ratio of carbohydrate to protein in the diet (Ari-manana and Leathwood, 1984; Li and Anderson, 1982). However, this ratio for the control group (X = 2.98; s.d. = 0.65; N = 16) and for the experimental group (X = 2.98; s.d. = 0.56; N = 16) were practically identical, suggesting that the carbohydrate/protein ratio is not relevant to the significant difference in the tyrosine ratio in the two groups.

Discussion and Conclusion

The result of this study shows that low TYR ratios are associated with depression only among the 54 year old women. For women who were 46 or 50 years old, there was no significant association. Also, regardless of age, low TYR ratios were associated with depression among those without menstruation. Seasonal difference was insignificant in considering the TYR ratio, in terms of both age and the presence or absence of menstruation. Low TRP ratios were not associated with depression. Both the amount of carbohydrate intake from the diet and the carbohydrate/protein ratio showed no significant relationship with depression.

The findings can be interpreted to mean that among physiologically older women, relatively less uptake of TYR from the diet, as compared with the other LNAA, leads to less NE in the neurons, resulting in depressive tendencies. In contrast, no such tendency was found for TRP. In this sense, the findings are in favour of the CA hypothesis rather than the IA hypothesis. However, this does not exclude the possible interpretation that depressed women eat less TYR, compared with the other LNAA. Due to the design of this study, a causal relationship cannot be established.

Another problem in comparing these two hypotheses is to know to what extent the TYR level in the serum affects brain 5-HT, and conversely, to what extent the TRP level affects brain NE. It is known that the intermediate precursors DOPA and 5-HTP decrease 5-HT and NE in the brain respectively (Everett and Borcherd-ing, 1970; Karobath et al, 1971; Lichten-steiger, 1967). At the same time, it is also known that administration of TYR or TRP is likely to be more specific in increasing NE and 5-HT respectively, and if this is correct, the results of this study may be in line with the CA hypothesis more clearly.

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Table 1.
The Mean Dietary Tryptophan and Tyrosine Ratios

Age and Menstruation	Experimental Group	Control Group	Significance Level (one-tail)	N
Dietary TRP Ratio				
3 Age Groups	.029 229	.029 274	n.s.	32
46 Year Olds	.029 512	.029 264	n.s.	6
50 Year Olds	.029 314	.029 395	n.s.	8
54 Year Olds	.029 097	.029 223	n.s.	18
Dietary TYR Ratio				
3 Age Croups	.103 747	.106 817	$p < .025$	32
46 Year Olds	.106 543	.106 367	n.s.	6
50 Year Olds	.102 644	.104 478	n.s.	8
54 Year Olds	.103 305	.108 006	$p < .025$	18
Menstruation				
Present	.104 281	.105 676	n.s.	15
Absent	.103 212	.107 761	$p < .025$	16