Xanthurenic Acid in Depression

The blank renal excretion, the spontaneous change or after Pyridoxine and correlation with anxiety and depression scales.

M.J.A.J.M. Hoes[1] and N. Sijben[2]

Summary

An altered or increased excretion of xanthurenic acid (XA) in urine for 24h after intake of 5 grams L-tryptophan (Trp) at 10:00 p.m. is considered a measure of strain in the organism. XA was studied in 104 hospitalized depressive patients (DSM-HI : 296.23; 296.33) and 15 controls. Zung anxiety and depression scales were rated. The XA-excretion after Trp load has a wider range than the blank XA-excretion. The XA-excretion has decreased after 1 week's treatment with antidepressants, but has not decreased any further after 2 weeks' treatment, unless pryidoxine is administered between week 1 and 2. The XA-excretion after 1 week shows some correlation (r-0.272; p = 0.021) with the level of anxiety, the psychic aspect of strain. Possible reasons for this weak correlation are discussed.

Introduction

The adaptational functions are subdivided into load, strain and stress (4, 7, 11). These terms are defined as follows. (Fig. 1): "Load is each burden due to internal or external factors that acts on the organism. Strain is the deformation that occurs in the organism under the influence of a load. One or several of the phenomena of strain will act as a signal to activate the adaptational process. Stress is the tension or counterforce that is induced in the organism to neutralize the changes of strain. All pathologic changes which are caused in the body by load are phenomena of strain". It is therefore important to have a measure of strain. One may think of the psychic aspect of strain, the free-floating anxiety (4, 7, 11, 13). A rough biologic measure of the strain is the excretion of xanthurenic acid (XA) in urine for 24 hours after the intake of L-tryptophan (Trp) at 10:00 p.m. (XA-test)(Fig. 2)(4, 9, 11). This procedure is called the XA-test. Trp is the parent substance of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). The co-enzymatically active form of vitamin B_6 (vitamin B_6*) is important in the aromatic amino acid decarboxylase, a major enzyme in the synthesis of serotonin[1]. Serotonin is an important neurotransmitter in the regulation of numerous homeostatic processes, e.g. sleep, body temperature and secretion of hypothalamic releasing factors (8).

The XA-test has been proposed as a test for strain, because it indicates the disorder in the Trp and Vitamin B_6* metabolism due to hypersecretion of glucocorticosteroids (14), some 2 deviations that disturb the synthesis of serotonin (1, 15, 16), which therefore — and because of the physiologic role of serotonin — become pathogenically significant. This test should be performed after one week of hospitalization. A disorder in the XA-test indicates that the strain causes secondary changes in the body by hypercor-ticism. For this same reason the strain may provoke a specific disorder in case of a disordered XA-test. The XA-test has been shown to be particularly disturbed in anxiety (3) and not in depression (2).

In the investigation on the significance of the XA-test as a measure of strain, some four

1. Lecturer for Biological Psychiatry
2. Research Psychologist, Department of Psychiatry Sint Radboud Hospital Catholic University of Nijmegen, THE NETHERLANDS.

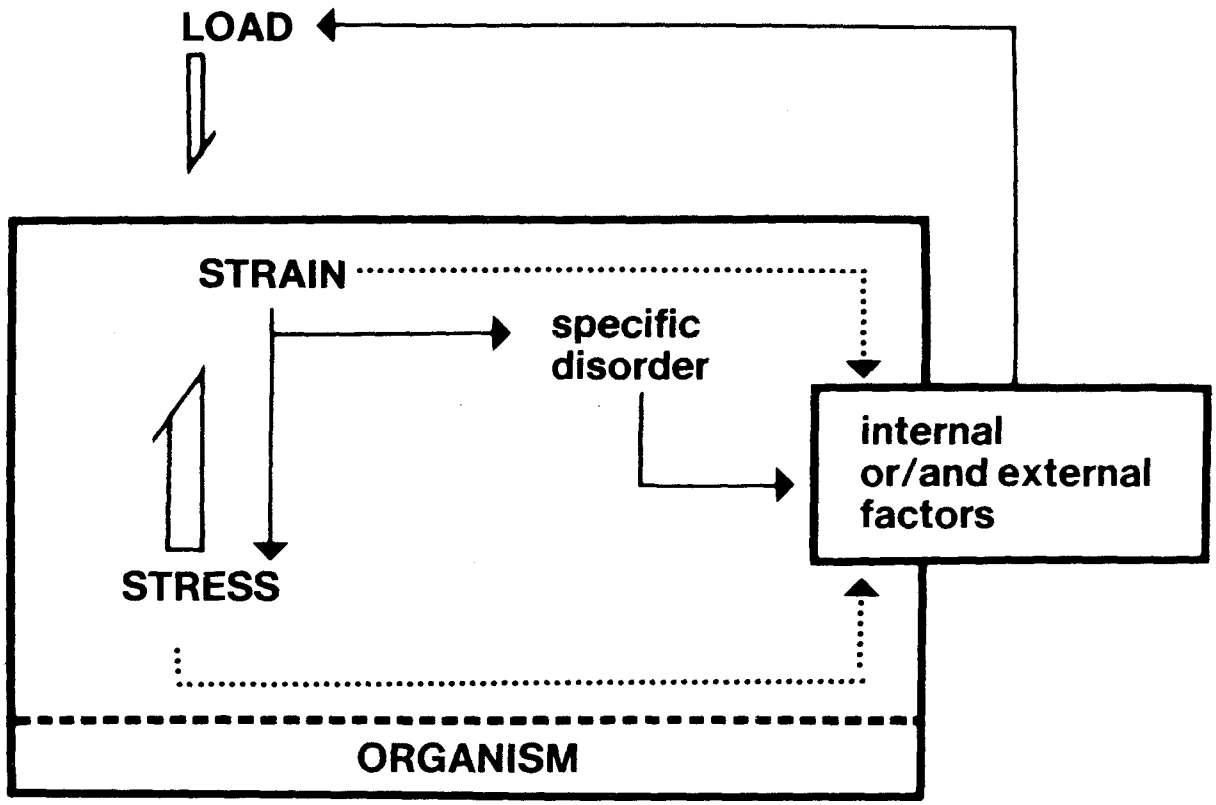

Figure 1 - THE LOAD-STRAIN-STRESS AND SPECIFIC DISORDER MODEL
In this model, only phenomena of strain may be of pathogenic importance to the organism, i.e. may provoke a specific disorder, syndrome or disease. As an internal factor, non-compensated strain or excessive stress forms a load for the organism.

problems remained which are described below. These studies were performed in patients with major depression, the depression being a presumed load.

1. A pilot study has demonstrated that the XA-test without or after Trp load differs significantly, in depressive patients (n = 13, p = 0.00046) as well as in volunteers (n=17, p = 0.00029)(Mann-Whitney-U-test)(9). The number of patients studied was low, so that this finding should be verified.
2. The XA-test is disturbed in depressive patients (2, 3). After 2 weeks of antidepressant therapy the XA-test in depressive patients (n=10) did not differ significantly from the reference values (6). At what time could the XA-test be performed at best?
3. A disturbed XA-test in depressive patients (n=10) is neutralized within 2 weeks' pyrodixine supplementation (6). Has the XA-excretion normalized after 1 week's Pyridoxine suppletion and is there a significant difference in the XA-excretion during the Pyridoxine supplementation, as compared with a corresponding period during treatment with antidepressants exclusively?
4. The XA-excretion is increased in patient with anxiety as primary diagnosis, either as anxiety-state (3) or hyperventilation syndrome (10). However, in depressive out-patients no correlation was found between the degree of free-floating anxiety, measured by means of the Zung anxiety-scale, and the XA-excretion (6). Is there a correlation between the degree of anxiety and the XA-excretion in more severely depressive (admitted) patients, either on admission, or during antidepressant treatment, whether or not combined with Pyridoxine supplementation? These four problems were investigated in the present study.

Material and Methods

The studied patients (n=104) complied

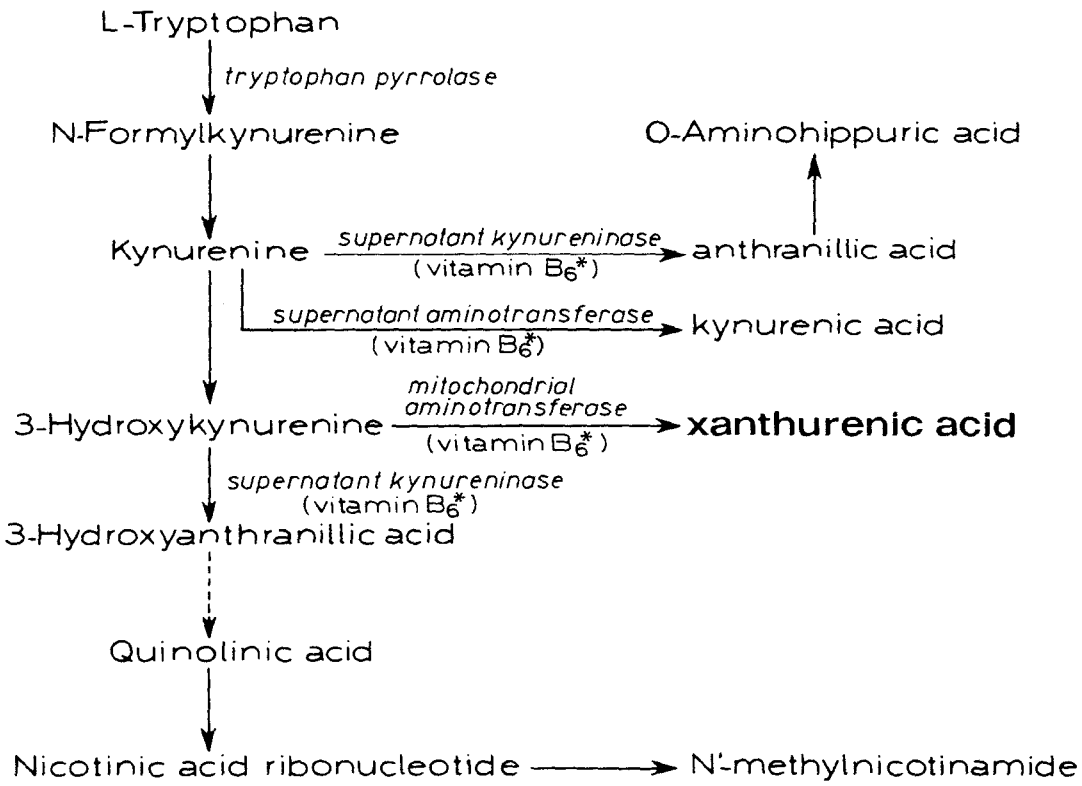

Figure 2 - THE L-TRYPTOPHAN NICOTINIC ACID RIBONUCLEOTIDE SYNTHESIS
A shortened version of nicotinic acid ribonucleotide (NAR) synthesis. The enzymes known to need the coenzymatically active form of vitamin B_6 (vitamin B_6*) are shown. To an absolute or relative (to diet) deficiency of vitamin B_6*, the mitochondrial aminotransferase is less sensitive, and the supernatant kynureninase the most sensitive enzyme. Corticosteroids induce the tryptophan pyrrolase and may cause a vitamin B_6* deficiency. By the sum of these 2 mechanisms, corticosteroids cause first a rise in the XA-excretion and then a drop in the XA-excretion as most severe pathology.

with the DSM-III* criteria for major depression, single episode, with melancholia (no. 296.23) or major depression, recurrent episode, with melancholia (no. 296.33). All patients were admitted for treatment of their depression, they all consented to participation in this study and, in the 4 weeks preceding the investigation as well as during the investigation itself, did not take any medication other than antidepressants, particularly no steroids. All patients were given antidepressants, either tricyclic drugs, or maprotiline (Ludiomil^R) in a dosage ranging from 75 to 150 mg daily. Healthy collaborators of the hospital Rivierenland at the 4 weeks preceding the study, they had not suffered from any minor illness, nor had they taken any drugs.

Urine was collected after intake of 5 g L-tryptophan at 10:00 p.m., and from 10:00 p.m. until 10:00 p.m. of the following day. The XA-concentration was determined spectrophotometrically (5) and the XA-excretion was expressed as micromoles/24h. The total intake of Trp in this XA-test was 5 g Trp at 10:00 p.m. and ± 1 g (from nutrition) during the following day, in total 6 g (29,378.64 micromoles/24h). The reference values of XA-excretion under these circumstances were 68.8 ± 19.0 micromoles/24h(m ± S.D.).

The degree of anxiety was determined by means of the Zung anxiety scale (ZAS) (18) and the degree of depression by means of the Zung depression scale (ZDS) (17). The ZA

*DSM-III: Diagnostic and statistical manual of mental disorders (1980) American Psychiatric Association, Washington D.C., 3rd ed. Tiel were the reference subjects (controls, n=15). During

and ZD scales were filled in at about 9:00 a.m. of the day after Trp intake.

The patients were subdivided into 4 groups *(AID)*. In groups A, B and C measurements were carried out before the clinical start of the antidepressant treatment (I), after 1 week of antidepressants (II) and after 2 weeks' antidepressants (III). In group D only the first measurement was performed.

Group A (n = 37) started a XA-test without Trp load on the evening of admission, and a XA-test after Trp load on the following evening. The controls underwent the same tests during two consecutive working-days. This procedure could only be repeated in a few patients as II and III.

Group B (n = 30) underwent the XA-test after Trp load and ZA and ZD scales were filled in, for I as well as for II and III. They were only treated with antidepressants.

Group C (n = 29) was evaluated by means of the same procedure as group B but was also given, besides antidepressants, Pyridoxine .HC1 (125 mg t.i.d.), between II and III.

Group D (n = 13) underwent the same procedure as group B but only for I.

Data collection was not complete in groups A, B and C.

Pearson correlation coefficients were calculated between XA, ZAS and ZDS; the differences in corresponding data between the groups were evaluated by means of Student's t-test and the effect of Pyridoxine sup-pletion on the XA-excretion was evaluated by means of variance analysis.

Results

The demographic data are represented per group in table I.

The XA-excretion (I) shows a range of 7-176 micromoles/24h in patients without Trp load and 13-3028 micromoles/24h after Trp load (n=104), whereas these values amount to 20-108 micromoles/24h c.q. 40-119 micromoles/24h in the controls. The reference values (m ± S.D.) after Trp load are 71.2 ± 18.8 micromoles/24h (n=15), almost identical to the reference values (68.8 ± 19.0 micromoles/24h) reported in a previous study (5). There is no significant sex difference in the XA excretion in the controls, either without or after Trp load (Mann-Whitney U-test). With regard to the reference values the XA-excretion is divided as follows: 0-33.6 micromoles/24 h (n = 8), 33,6-108.8 micromoles/24 h (n = 51) and > 108.8 micromoles/24 h (n = 45).

The XA-excretion without and with Trp load (group A) is given in table II.

There is a significant difference between the values without and with Trp load both in patients (Wilcoxon matched pairs signed ranks test z =-4.840, $p<0.0001$ for I n = 35) and in controls (z = 2.414,p = 0.016 for n=15).

There is no difference between patients and controls as to the values with load (z= 1.229, p = 0.097), but there is a difference as to the values without load (z= 1.636, p = 0.009; Kolmogorov-Smirnov 2-sample test). The standard deviations in the diverse groups are very large and differ greatly from each other so that non-parametric tests are used. A significant correlation was found in the XA excretion between I and II in the patients without (r = 0.94 p = 0.001) as well as with (r = 0.57, p = 0.04) Trp load.

The XA-excretion, ZAS and ZDS of patients without Pyridoxine suppletion between II and III is given in table III. There is no significant correlation between the XA-excretion and ZAS or XA-excretion and ZDS at I, II or III.

The XA-excretion values at I, II and III do not differ significantly (Friedman analysis or variance X^2 = 4.98 p = 0.083). At all three measuring times, the XA value differs from the control value (Kolmogorov-Smirnov 2 sample test I: z= 1.88, p = 0.002; II:z= 1.55, p = 0.016, III: z=1.44, p = 0.032). The ZAS values differ significantly between I-II (p = 0.005), I-III ($p<0.001$) and II-III ($p=0.014$). The ZDS values differ significantly between I-II (p = 0.03), I-III (p = 0.001) and II-III (p = 0.005).

The XA-excretion, ZAS and ZDS of patients with Pyridoxine suppletion between II and III (Group C) is given in table IV. There is no significant correlation between the XA-excretion and ZAS or XA-excretion and ZDS at I, II or III. The XA-excretion differs significantly between I-III ($p<0.05$ and II-III (p = 0.04)

At I and II, the XA-excretion values differ significantly from those of the controls (I:z= 1.85, p = 0.002; II:z= 1.85, p = 0.002; Kolmogorov-Smirnov 2-sample test).

The ZAS values differ significantly between I-III ($p<0.001$)and II-III (p = 0.009). The ZDS values differ significantly between

TABLE I
DEMOGRAPHIC VARIABLES OF THE PATIENTS IN THE GROUPS

	AGE (years)			SEX		n
GROUP	m	±	S.D.	m	f	
A	48.56	+	15.65	13	24	37
B	47.59	+	17.86	13	28	41
C	41.90	±	17.56	7	22	29
D	46.92	±	17.86	6	7	13
CONTROLS	29.87	±	7.37	9	6	15

In groups A, B and C women are preponderant, in group D there are almost as many men as women, whereas there are more male than female controls. The total number of participating patients is 104. Fifteen patients of group B also belong to group A or D and one person of group A also belongs to group D.

TABLE II
XANTHURENIC ACID EXCRETION (XA) WITHOUT AND AFTER LOADING WITH 5 G L-TRYPTOPHAN AT 10:00 P.M. (GROUP A)

DEPRESSIVE PATIENTS	**XA (micromoles/24th) WITHOUT LOAD**			**AFTER LOAD**		
	m	**±**	**S.D.**	**m**	**±**	**s.D.**
I (start) n =	37.17	± 35	30.25	156.64	+ 36	199.65
II (1 week) n =	59.00	+ 8	67.73	124.00	+ 10	130.98
III (2 weeks) n =	32.60	± 5	9.26	83.00	± 5	34.08
CONTROLS n =	50.33	± 15	19.33	71.20	± 15	18.79

There is a significant difference between the blank and loaded values, both in the patients (I: $p = 0.001$) and in the controls ($p = 0.014$). The difference between the loaded and blank values is based on the excess of substrate found in the sideline of the NAR synthesis. The differences between the values of patients and controls are significant for the blank values but not for the values after Trp load ($z = 1.636$, $p = 0.009$ vs. z 1.229, $p = 0.097$. Kolmogorov — Smirnov 2 — sample test). The S.D. of the values after Trp load are however very large.

TABLE III

XANTHURENIC ACID EXCRETION (XA), ZUNG ANXIETY SCALE (ZAS) AND ZUNG DEPRESSION SCALE (ZDS) IN PATIENTS BEING TREATED WITH ANTIDEPRESSANTS BUT WITHOUT PYRIDOXINE SUPPLETION (GROUP B)

	XA (micromoles/24h)			ZAS			ZDS		
Depressive Patients	m	±	S.D.	m	±	S.D.	m	±	S.D.
I (start) n =	190.78	+ 41	215.29	51.14	29	8.77	51.90	± 29	9.90
II (1 week) n =	139.11	± 39	117.01	45.44	+ 27	10.85	47.93	+ 27	10.63
III (2 weeks) n =	127.03	± 33	117.88	42.96	+ 27	9.65	45.48	+ 27	10.95
CONTROLS n =	71.20	± **15**	18.79						

The XA excretion does not change significantly between I, II and III and does not reach the control values. The ZAS values differ significantly between HI (p = 0.005), I-III (p 0.001) and II-III (p = 0.014). The ZDS values differ significantly between I-II (P = 0.03), I-III (p = 0.001) and II-III (p = 0.05).

TABLE IV

XANTHURENIC ACID EXCRETION (XA), ZUNG ANXIETY SCALE (ZAS) AND ZUNG DEPRESSION SCALE (ZDS) IN PATIENTS BEING TREATED WITH ANTIDEPRESSANTS AND WITH EXTRA PRYIDOXINE SUPPLETION BETWEEN 1-2 WEEKS' ANTIDEPRESSANT THERAPY (GROUP C)

	XA (micromoles/24h)			ZAS			ZDS		
Depressive Patients	m	±	S.D.	m	±	S.D.	m	±	S.D.
I (start) n =	321.17	+ 29	632.83	48.08	± 26	8.56	53.81	+ 26	9.59
II (1 week) n =	193.00	± 29	295.61	45.38	± 29	9.80	47.24	± 29	12.11
III (2 weeks) n =	75.52	± 27	45.09	40.70	± 27	9.66	43.63	± 27	10.83
CONTROLS n =	71.20	+ 15	18.79						

The XA-excretion changes significantly between I-II (p = 0.05) and II-III (p = 0.04). The ZAS values differ significantly between I-III (p = 0.001) and II-III (p = 0.009). The ZDS values differ significantly between I-II (p = 0.02), I-III (p = 0.001) and II-III (p = 0.004). The XA-excretion indicates that Pyridoxine suppletion improves the deviation in the main line of the NAR synthesis and hence diminishes the production and excretion of XA.

III ($p = 0.02$), I-III ($p<0.001$) and II-III ($p = 0.004$).

When combining groups B and C a significant correlation is found between the XA-excretion and ZAS at II ($r = 0.272$; $p = 0.021$, $n = 56$). When comparing the XA-excretion values at II and III between groups B and C (without and with Pyridoxine suppletion respectively) the change between II and III in the group with Pyridoxine suppletion appears significant. From the above given results it appears that there is no more significant difference with the controls in group C at moment III, whereas the difference is still significant in group B. When the values are compared with each other by means of variance analysis (B III and C III) the difference indeed is significant ($F = 5.211$, $p = 0.026$).

Discussion

The questions formulated in the introduction can be answered on the basis of the obtained results.

With regard to question 1 about the difference between XA-excretion without and after Trp load, these values differ significantly in the controls as well as in the patients. These results confirm the previous findings (9). Because the range of XA-excretion after load (13-3,028 micromoles/24h) is wider than without load (7-176 micromoles/24h) in patients, loading with Trp is to be preferred.

As to question 2, a significant difference in the XA-excretion after 1 week of antidepressant treatment (I-II) does not exist. The S.D. of the XA-test has diminished after 1 week, so that the changes that occur make the result of the group as a whole more homogeneous. Admission to a hospital causes hypersecretion of glucocorticosteroids; this hypersecretion has returned to the patient's baseline level after 1 week of hospitalization (12). This extra secretion of glucocorticosteroids might explain the greater variability in the XA-test results at admission. So, the XA-test should be performed after 1 week of admission.

As to question 3, supplementation of Pyridoxine (125 mg t.i.d.) between 1-2 weeks of antidepressant treatment causes a significant drop in the XA-excretion ($n = 27$; $p = 0.04$) and normalizes the XA excretion. In the patients without Pyridoxine supplementation ($n = 33$) no further drop in the XA-excretion occurs between weeks 1-2. Supplementation of Pyridoxine causes no significant extra effect on the anxiety or depression scores compared with no supplementation during the same period ($n = 27$ vs 27), although the change in the depression score seems greater in the Pyridoxine supplemented group ($p = 0.05$ vs 0.004).

As to question 4, a significant correlation between the XA-excretion and anxiety can only be found when groups B and C are combined after 1 week of treatment ($r: 0.272$; $p = 0.021$; $n = 56$). This conforms with the prediction on the basis of the load-strain-stress model.

Factors that may have impeded the finding of this correlation and may have weakened the correlation found, can be indicated. The range of the XA-excretion (13-3,028 micromoles/24h) is much larger than that of the ZAS (20-80 points). A second problem is the fact that the XA-excretion is more disturbed in the lower range (0-33,6 micromoles/24h) than in the higher range (> 108, 8 micromoles/24h). This implies that the pathology actually falls apart into 2 pieces. However, upon increasing anxiety, the ZAS increases linearly. The fact that after 1 week of admission a correlation is found, is important because at that time one does not measure extra strain effects, due to the admission enhanced secretion of glucocorticosteriods (12).

Acknowledgements

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