Hyperventilation Syndrome, Treatment With L-Tryptophan and Pyridoxine; Predictive Values of Xanthurenic Acid Excretion.

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Abstract

A case is made for the pathophysiological importance of the cerebral serotonergic neurons in the hyperventilation syndrome (HVS). Their function depends on the systemic L-tryptophan metabolism.

The role of L-tryptophan metabolism is studied in 13 HVS patients, by administration of pyridoxine 125 mg t.i.d. and L-tryptophan two grams for four weeks. The xanthurenic acid excretion (XA) is measured as an index of the peripheral L-tryptophan metabolism, before treatment. The treatment resulted in freedom of hyperventilation attacks in nine patients. The XA was elevated or low in eight and normal in one of the nine responders and normal in the four non-responders.

The extremes in the XA excretion had disappeared after treatment. Treatment results and XA data indicate that the L-tryptophan metabolism is important in the pathophysiology of the HVS, and that the XA discriminates responders from non-responders to pyridoxine, L-tryptophan treatment.

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Introduction

The hyperventilation syndrome (HVS) is a functional syndrome (van Dis, 1978) caused by stress (Hermann et al., 1978). Important features of the HVS are the increased respiration, the anxiety, and an often occipitocervical headache and muscular hypertonia (Hardonk and Beumer, 1979; van Dis, 1978).

The cerebral serotonergic neurotransmission (CST) is important to these symptoms on the basis of the following evidence from animal experiments: CST activates the inhibition of respiration that is found during an acute alcohol intoxication (Smith et al., 1975) or during Slow-Wave-Sleep (Jouvet, 1972). Animals depleted of serotonin have been used as experimental models of anxiety (Ellison, 1975). CST is important in the inhibition of pain (DeSousa and Wallace, 1977; Hoes, 1979-c). CST inhibits muscle tone as a result of an inhibition of afferent input (Hoes, 1979-c), a stimulation of Ren-shaw interneurons (Meyers-Lohman, 1971) and a suppression of monosynaptic reflexes (Clineschmidt and Andersen, 1970). Because of this evidence, underactivity of the CST is proposed as a pathophysiological model for HVS. As a matter of fact, the effectiveness of clomipramine in HVS was explained by its

enhancement of the CST (Hoes et al., 1980-a).

The CST is dependent on the cerebral synthesis of serotonin from L-tryptophan. The rate-limiting step in this process is the cerebral uptake of L-tryptophan from the blood plasma (Fernstrom and Lytle, 1976). The plasma concentration of L-tryptophan is lowered by a diet short of L-tryptophan, or by increased utilization of L-tryptophan in i.e. the biosynthesis of nicotinamide (NiA) (Figure 1).

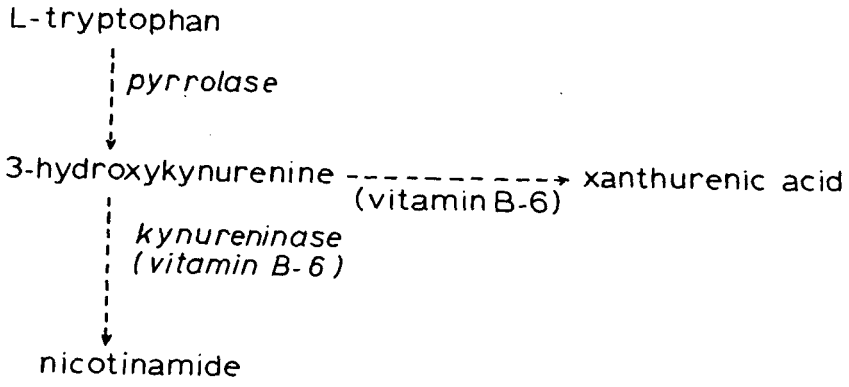

FIGURE 1

L-TRYPTOPHAN-NICOTINAMIDE BIOSYNTHESIS A shorthand version of the nicotinamide biosynthesis. Hypercorticism induces the pyrrolase; enhanced pyrrolase activity will pull more L-tryptophan in this synthesis, activating the pyridoxal-5-phosphate containing enzymes (vitamin B6). This activation by substrate and the induction of other pyridoxal-containing enzymes by hypercorticism, leads to a relative pyridoxal-deficiency. To this pyridoxal-deficiency the kynureninase is the most sensitive enzyme in the nicotinamide biosynthesis. The xanthurenic acid excretion will rise by the enhanced pyrrolase and diminished kynureninase activity. The xanthurenic acid excretion may eventually diminish, only when not enough pyridoxal is available for the mitochondrial transaminase in the xanthurenic acid side-chain, this enzyme being less sensitive to a pyridoxal-deficiency.

A good diet supplies about one gram of L-tryptophan a day. Man synthesizes about 12-15 mg NiA a day. For the synthesis of one mg of NiA, 60 mg L-tryptophan are needed. So, man needs 720-900 mg of L-tryptophan a day for his NiA synthesis. Two thirds of his daily NiA-requirements are covered by his own synthesis; the remaining one third is covered by uptake from the food. Thus, the NiA synthesis is the major metabolic pathway for L-tryptophan in the body (Bogert et al., 1973).

Increased utilization of L-tryptophan in the NiA synthesis is caused by induction of the pyrrolase; this is notably caused by glucocorticosteroids (Green, 1978). This induction of the pyrrolase may engender a considerable loss of L-tryptophan from the systemic circulation, and thus deprive the cerebral serotonin synthesis of its mother-substance (Curzon, 1969; Hoes, 1980; Moussaoui, 1978).

The functional state of the NiA biosynthesis is studied by measuring the urinary excretion of intermediates such as 3-hydroxyky-nurenine, or side-chain products such as xanthurenic acid (XA), after oral intake of a loading dose of L-tryptophan (Hoes et al.,

1980-b). The excretion of XA in this loading test, is elevated in anxiety, and this is explained by effects of elevated glucocorticoid plasma concentrations on the NiA synthesis (Hoes, 1979-a). HVS patients are anxious in general, and so one expects that HVS patients will have an elevated XA excretion in the L-tryptophan loading test.

When the HVS patients have an elevated XA excretion, this indicates that they derive L-tryptophan from the cerebral serotonin synthesis. Since underactivity of the CST is proposed as pathophysiological mechanism of HVS, an elevated XA excretion indicates a positive feedback in the HVS pathophysiology as long as the anxiety persists. As a matter of fact, Lewis (1959) proposed on clinical evidence in his model of sequence of events characterizing the HVS, that apprehension reinforces the HVS (Figure 2). The HVS provokes a hypocapnia, the hypocapnia aggravates the HVS symptomatology, the perception of these symptoms leads to apprehension and this apprehension reinforces the HVS.

If the peripheral metabolism is that important to the pathophysiology of the HVS, then two predictions should be investigated:

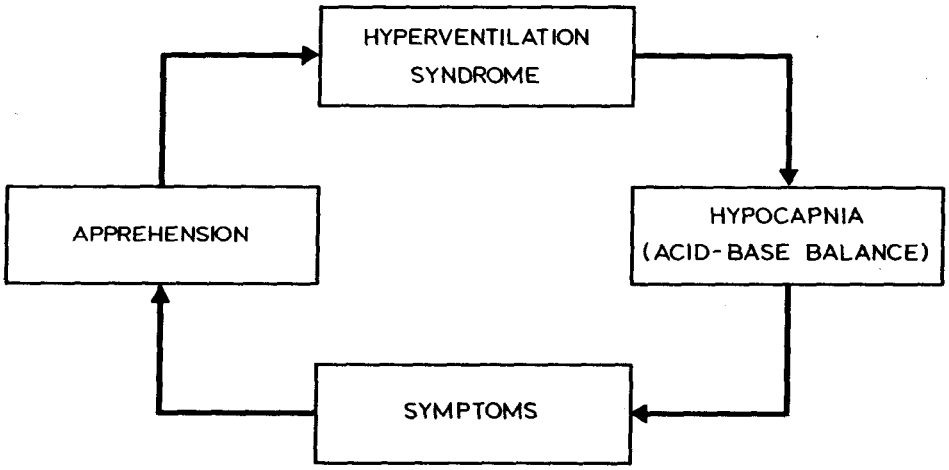

FIGURE II

SEQUENCE OF EVENTS CHARACTERIZING HYPERVENTILATION SYNDROME (after Lewis, 1959).

The disorders in the L-tryptophan metabolism facilitate the different steps in the sequence, inducing a positive feedback in the development of the disorder. (See text, under discussion.)

1) In HVS patients the excretion of XA in a L-tryptophan loading test is disturbed.

2) HVS patients are cured by orthomolecular treatment aimed at two points:

a) Correction of the XA-excretion. Pyridoxine 125 mg t.i.d. during four weeks will suffice (Hoes, 1979-b).

b) Supplementation of L-tryptophan to correct any L-tryptophan-deficiency state. Two grams of L-tryptophan are sufficient (Hoes, 1979-b).

Patients and Methods

Thirteen patients (4f, 9m; age: 34.5+9.2 yrs, range 22-56 yrs) were selected according to the HVS criteria specified elsewhere (Folgering and Colla, 1978). Patients with another psychiatric diagnosis but anxiety neurosis according to the Feighner criteria (Feigh-her et al., 1972) were excluded, as were patients taking oral contraceptives or other hormones. First, the XA excretion was meas-ured

in urine, collected during 24 hours after oral intake of 5 grams of L-tryptophan at 22.00 hours, as described previously (Hoes, 1979-a; Hoes et al, 1980-b). Then the patients received pyridoxine 125 t.i.d. + L-tryptophan 2 g vesp., both for four weeks, as described previously (Hoes, 1979-a). During the fifth week they were interviewed about their frequency of attacks and HVS symptoms (Folgering and Colla, 1978). The L-tryptophan loading test was repeated if abnormal at the first time or if the treatment had resulted in an absence of attacks for at least the last week.

At the time of these experiments the only available reference values of the XA excretion were those of 648 neurologic and psychiatric patients. Many of these persons may not have suffered any condition influencing the XA excretion. The XA values are however positively skewed, with a modus of 50 *u*mol/24 hours and a median 78 *u*mol/24 hours. On the basis of the distribution curve, 40-120 *u*mol/24 hours (n=347) was considered normal. Recently the XA excretion could be investigated in healthy volunteers, 68.8±19.0 *u*mol/24 hours (n=31), median 70 *u*mol/24 hours, range 82 *u*mol/24 hours (Hoes et al, 1980-b). The determination method of XA by spectrophotometry is accurate (Hoes et al, 1980-b).

During their first visit to the out-patient department, all patients were checked for diabetes mellitus by determination of the fasting plasma-glucose concentration and of glucose and ketone bodies in the morning urine.

Statistical analysis was performed by Student t-test and the Moses test of extreme reactions.

Results

The patients included in this study suffered 0.5-3 years from HVS, and had at least two attacks/week during the last two months before treatment.

Of the 13 patients, nine were symptom-free after three weeks of treatment (3f, 6m) and four were not so (1f, 3m) (Table 1). The mean age of the responders (37.1 ±10.1 years) does not differ significantly by t-test (p=0.069) from the age of the non-responders (28.8±2.2 years) (Table 2). The L-tryptophan loading test had to be repeated just in the responders whereas the non-responders excreted normal amounts of XA (Table 3). All checks for diabetes mellitus were normal in all 13 patients.

The XA-excretion in the responders is high (n=5), low (n=3) or normal (n=1). After treatment one high excretor (nr.3) is still high, while one low excretor (nr.7) excretes a high amount XA. Because a parametric approach like the the t-test, addressed at differences in central tendency, does not take account of the pathological extreme low and high values, the Moses test of extreme reactions is most appropriate (Siegel, 1956). Furthermore the t-test is not permissible be cause the distribution of the XA-values of the patient group is evidently non-normal and there is too great a difference between the variances of the treatment responders and the reference group (coefficient of variance 1.01 vs 0.25). The pre-treatment values of XA differ significantly from the reference values ($p(sh< n_c\text{-}2h+g)=0.00003$). The properly different values are exclusively found in the responder group. The XA excretion values of the nine responders after the treatment differ significantly from the pre-treatment values (Moses test: p=0.025), i.e. extreme low and extreme high values tend to disappear. The post-treatment values do not differ significantly from the reference values, viz. in extreme reactions (Moses test: p=0.50).

The nine treatment responders received no further medication after the four trial weeks; they remained symptom-free during a three months follow-up.

Discussion

This is an open study and the number of patients studied is small. The data are however relevant for discussion.

The XA-excretion shows two types of disorder; it is either too high or too low. Since either disorder is corrected by the pyrid-oxine-L-tryptophan treatment, the supply of the substrate L-tryptophan is not important to this normalizing effect, but the pyridoxine is. Two enzymes are relevant, both containing the active principle of pyridoxine, pyrid-

oxal-5-phosphate (PAL), as co-factor (Figure 1). These two are the supernatant enzyme kynureninase and the mitochondrial trans-aminase in the XA side-chain. The apo-enzyme-cofactor (PAL) binding-constant is weaker for the kynureninase than for the transaminase (Adams et al., 1976; Green et al., 1978). So, in any PAL disorder, corrected by pyridoxine supplementation, the excretion of XA in a L-tryptophan loading test will first rise and then fall, compared to the reference values, and during more pronounced PAL disorders it will fall. The low XA-ex-cretion thus is the most pathological of the two XA disorders.

Each disorder in the XA-excretion is caused either by competitive inhibition of the PAL binding sites of the enzymes, or by a PAL de-ficiency. Competitive inhibition of PAL bind-ing sites has been described for steroid hor-mones (Mason et al., 1969). Because the HVS is a stress disorder, glucocorticoster-oids will be hypersecreted (Selye, 1976), intermittently during attacks or chronically; however, they were not measured in this study. But for glucocorticosteroids no competitive inhibition of the kynureninase has been described in the literature. The transaminase has even a more stable apo-enzyme-cofactor binding and is better protected in the mitochondrion against competitive inhibition than the supernatant kynureninase. So, in any case, the mitochondrial transaminase will be better protected against the influence of glucocorticosteroids than the kynureninase. Competitive inhibition in general can also be exerted by metabolic products; thus, the NiA inhibits the pyr-rolase by endproduct inhibition. No inhibition of enzymes by substrate has been described for PAL-containing enzymes in the NiA synthesis, neither by the endproduct NiA (Schepartz, 1973).

The disorder in the XA-excretion must be explained by PAL deficiency.

The PAL deficiency has not a dietary source, because the diet of the patients was adequate, supplying the required 2 mg pyridoxine a day (Bogert et al., 1973). A PAL deficiency occurs also when PAL-containing enzymes are activated by augmented supply of substrate (Wynne, 1975), or if the synthesis of PAL-containing enzymes is induced directly by e.g. hormones (Schepartz, 1973). In HVS, both mechanisms can occur by enhanced secretion of glucocorticosteroids. These hormones induce the pyrrolase (Figure 1), the rate-limiting enzyme of the NiA synthesis; thus more L-tryptophan is pulled into this synthesis, activating PAL containing enzymes (Curzon, 1969; Green, 1978), and lowering the PAL levels in serum (Green et al., 1978). Furthermore, glucocorticosteroids induce the synthesis of PAL-containing enzymes, such as the tyrosine transaminase, tryptophan transaminase, alanine transaminase or aromatic amino acid decarboxylase. The kynureninase is not induced. Thus the total body supply of PAL will be lowered. To such PAL consuming activities the dietary intake will soon yield, because the required 2 mg a day are just supplied by a regular diet (Bogert et al, 1973). In pyridoxine loading studies 60 percent of a physiological dose of pyridoxine is recovered in the subsequent 24 hours urine (Wozenski et al., 1980) and 35 percent of a megadose of 750 mg (O'Reilly et al., 1980). The initial distribution phase of pyridoxine and PAL has a $t^1/_2$ of two hours; the $t^1/2$ of the elimination phase could not exactly be computed (O'Reilly et al, 1980). One can conclude that the body does not have any pyridoxine pools of any importance. Thus, a relative (to the adequate diet) pyridoxine and PAL deficiency is to be considered the causative factor for the disordered XA-excretion. The plasma concentration of L-tryptophan will be lowered as soon as the pyrrolase is induced by the glucocorticosteroids because thus L-tryptophan will be pulled into the NiA synthesis from the systemic circulation (Curzon, 1969; Hoes, 1980; Moussaoui, 1978). This is illustrated by the elevated XA-excretion in a L-tryptophan loading test in women using oral contraceptives (o.c). They had no confirmative signs of a pyridoxine deficiency (Adams et al., 1976), and the XA elevation had to be explained by induction of the pyrrolase.

However, Green et al., (1978) measured the plasma concentrations of L-tryptophan and the XA excretion during the same L-tryptophan loading test in women on o.c. They

found an elevated XA excretion but refute an induction of the pyrrolase as explanation, because they found a comparably large area under plasma tryptophan versus time curve in their patients than in controls. But there are two contra-arguments: First, any deficiency of L-tryptophan in the diet can be counteracted by increased mobilisation of L-tryptophan from body-protein (Niskanen et al., 1976). Secondly, in the figure of Green et al., the curve of plasma concentrations of L-tryptophan in the o.c. users stays under that of the controls! More important is that the plasma concentration of L-tryptophan at the end of the absorption phase is in the figure significantly ($p<-0.05$) lower for the o.c. users than for the controls, although Green et al. claim that the area under the curve is the same. The difference in the absorption peaks cannot be explained by altered elimination kinetics, because the descending parts of the curves of controls and o.c. users run strictly parallel. So, the absorption peak differs because L-tryptophan reaches the systemic circulation more slowly in the o.c. users than in the controls. Altered gut movements or gut absorption kinetics are not described in o.c. users, to account for the difference in L-tryptophan kinetics. The second possibility is the first pass effect through the liver. If in o.c. users more L-tryptophan is pulled into the liver than in controls, this means that the pyrrolase activity in the o.c. users has been enhanced. Definite separation of a pyrrolase-and a PAL effect require the execution of a L-tryptophan and kyn-urenine loading test (Wolf et al., 1980).

The described disorders of the L-trypto-phan-NiA metabolism can sustain the HVS symtomatology in several ways. This is best understood according to the sequential steps in the HVS model of Lewis (Figure 2).

1) The pathophysiology of the HVS of underactive CST is reinforced by the loss of L-tryptophan from the systemic circulation into the liver by the pyrrolase pull. When besides the plasma concentrations of kynurenine rise, the kynurenine may inhibit the cerebral uptake of L-tryptophan, although this effect probably is small in man (Green, 1978).

2) The next mechanism concerns the acid-base balance. Patients with an elevated XA excretion can show a diabetes mellitus-like state. This is explained either by complex forming of the elevated XA with insulin, thus inactivating the latter (Rose et al., 1975); or by diminished production of quinolinic acid, an intermediary product in the NiA synthesis from below the kynureninase step. Quinolinic acid is an inhibitor of the hepatic phosphoenolpyruyatecarboxykinase, an important enzyme in the gluconeogenesis (Adams et al., 1976). These hyperglycemic patients can develop a ketosis. A ketosis facilitates the hyperventilation and neuromuscular irritability symptoms. The experience of this reinforcement can evoke apprehension. The disorder in L-tryptophan and glucose metabolism is completely restored by pyridoxine suppletion (Adams et al., 1976; Rose et al., 1975). This derangement can however induce a positive feedback, because in animal experiments it was shown that hyperglycemia induces the described disorder in the NiA metabolism, with enhanced XA excretion (Akarte and Shastri, 1974)!

3) The apprehension can be reinforced by diminished production of NiA, the ketosis aside. NiA was shown in recent experiments to possess benzodiazepine-like action and benzodiazepines are antianxiety drugs (Mohler et al., 1979). The HVS patients studied did not show signs of a fullblown clinical (Bogert et al., 1973) or subclinical (Green, 1973) pellagra. Yet when the patients have a PAL disorder, as proved by the therapeutic effect of the pyridoxine (and L-tryptophan) suppletion in this study, the production of endogenous NiA ($^2/3$ of the total requirements) is diminished. Besides, anxiety is a prominent feature of HVS and of subclinical pellagra.

TABLE 1

SEX OF THE HVS PATIENTS

	SEX	
	f	**m**
RESPONDERS	**3**	**6**
NON – RESPONDERS	**1**	**3**
TOTAL	**4**	**9**

There is no significant difference by t-test in sex between the patients who responded and who did not respond to treatment.

4) As long as the apprehension (and anxiety) persist, the elevated glucocorticoster[1] oid secretion will keep the pyrrolase activity induced, deriving more L-tryptophan in the NiA synthesis. The augmented supply of substrate keeps the PAL containing enzymes hyperactivated, thus further emptying the PAL stores in the body. By this mechanism a positive feedback is introduced in the L-tryptophan derivation, because the brain is deprived of steadily more L-tryptophan and the anti-anxiety substances serotonin (Ellison, 1975) and NiA (M6hler et al., 1979).

In the patients studied, the possibilities two and three are excluded as a reinforcement of the HVS, because the fasting glucose levels in plasma were normal and the fasting morning urine was negative for glucose and ketone bodies. The possibilities one and four reserve however serious consideration in the treatment responders.

The treatment responder with a normal preteatment excretion of XA, probably has had a disturbed CST in view of his therapeutic response. His normal excretion of XA is either an accidental finding, or the turning point in XA excretion from a high to a low excretor of XA, possibly the reserve.

In the four non-responders to treatment, the XA excretion was normal. Both findings argue against a disorder in the L-tryptophan metabolism and the CST. In these patients the CST was functionally deranged during the HVS attacks, but not permanently exhausted.

Summarizing, this study shows that there is a group of HVS patients with a disturbed peripheral L-tryptophan metabolism. This disorder measured by the XA excretion in a L-tryptophan loading test is however not specific for HVS patients (Hoes, 1979-a, 1979-b); a low XA excretion is more pathological than a high one. Any XA disorder is perfectly correlated with a favorable response to the pyridoxine + L-tryptophan treatment.

So, one can conclude that because there are HVS patients with a disturbed XA excretion, and because the XA disorder accurately predicts the therapeutic response of the HVS to the orthomolecular treatment by pyridoxine and L-tryptophan, the pathophys-iology of underactive CST in the HVS is considerably strengthened.

Further study along this line should include L-tryptophan and kynurenine loading tests (Wolf et al., 1980), determinations of plasma Cortisol (Selye, 1976) and quantification of respiration parameters (Folgering and Colla, 1978).

TABLE II

AGE OF THE HVS PATIENTS

	AGE (years)			
	m	±	S.D	
RESPONDERS (9)	**37.1**		**10.0**	
NON-RESPONDERS (4)	**28.8**	**2.2**	**34.5**	**9.2**
TOTAL (13)				

There is no significant difference by t-test in age between the patients responded and who did not respond to treatment. The age-range for all patients (N=13) is 22-56 years.

TABLE III

XANTHURENIC ACID EXCRETION OF HVS PATIENTS

	XANTHURENIC ACID (XA) (*u*mol/24 hrs)		
	1	**2**	
RESPONDERS			
1	**597**		**93**
2	**543**		**51**
3	**494**		**210**
4	**180**		**85**
5	**147**		**67**
6	**107**		**87**
7	**23**		**139**
8	**21**		**76**
9	**14**		**78**
NON-RESPONDERS			
i	**109**		
2	**91**		
3	**85**		
4	**48**		
TOTAL			
MEDIAN	**107**		**85**
RANGE	**583**		**159**
N	**13**	**9**	

The excretion of XA in 24 hours urine after oral intake of 5 grams of L-tryptophan was measured. This was done in all patients before (1) treatment; it was repeated after (2) treatment, only if it had been abnormal the first time or if the therapeutic response had been favorable. At the time of these experiments the range of XA excretion considered normal was 40-120 *u*mol/24 hrs. So, the first 5 values in the responder group are elevated, the 6th is normal and the last 3 are low. The non-responders show just normal values.

Statistics:

The statistical analysis was performed by P. Colla and N. Sijben, research psychologist, Dept. of Psychiatry, Radboudhospital.

Note:

This paper is an adaption of a lecture delivered at the symposium of the Dutch Hyperventilation Study Croup, Utrecht, 19 October, 1979, by Hoes.

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