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Biochemical Investigations into the Alcoholic Delirium: Alterations of Biogenic Amines*

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Summary. In eight male patients with alcoholic delirium concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovannilic acid (HVA) in CSF, activity of dopamine-β-hydroxylase (DBH), and urinary excretion of noradrenaline (NA), adrenaline (A), and dopamine (DA) were measured during the delirium and a drug-free control period.

MHPG concentration in CSF, excretion of NA and A as well as activity of serum DBH were significantly elevated during the delirium phase as compared to the control period. Urinary DA excretion and HVA in CSF did not show any constant changes. There was a positive correlation ($r = 0.64$) between DBH activity and the intensity of the delirium (as measured on the delirium rating scale).

It is hypothesized that there is a relationship between alcoholic delirium and increased central noradrenergic activity.

Key words: Alcoholic delirium – 3-Methoxy-4-hydroxyphenylglycol – Homovanillic acid – Dopamine-β-hydroxylase – Noradrenaline – Adrenaline – Dopamine.

Zusammenfassung. Bei 8 männlichen Patienten mit einem Alkoholdelir wurde während des Delirs und einer medikationsfreien Kontrollperiode die Konzentration von 3-Methoxy-4-hydroxyphenylglycol (MHPG) und Homovanillinsäure (HVA) im Liquor cerebrospinalis, die Aktivität der Dopamin-β-hydroxylase (DBH) im Serum sowie die Höhe der Noradrenalin(NA)-, Adrenalin(A)- und Dopamin(DA)-Ausscheidung gemessen.

Während des Delirs waren die MHPG-Konzentrationen im Liquor, die NA- und A-Ausscheidung im Urin und die DBH-Aktivität im Serum signifikant höher als während der Kontrollperiode. Die DA-Ausscheidung sowie die Konzentration von HVA im Liquor zeigten keine konstanten Verände-

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rungen. Zwischen der Höhe der DBH-Aktivität und der Intensität des Delirs (gemessen auf einer Delir-Einschätzungsskala) bestand eine positive Korrelation ($r = 0.64$).

Es wird die Hypothese vertreten, daß zwischen der Symptomatik des Delirium tremens und zentraler noradrenerger Erregung kausale Beziehung besteht.

Schlüsselwörter: Delirium tremens – 3-Methoxy-4-hydroxyphenylglycol – Homovanillinsäure – Dopamin-β-hydroxylase – Noradrenalin – Adrenalin – Dopamin.

Introduction

Withdrawal symptoms are considered a reflex hyperactivity of those functions in the central nervous system which were previously inhibited by alcohol (Kalant, 1961). This hypothesis was used by Wieser (1965) to explain the ethiopathogenesis of the alcoholic delirium. He called this the 'theory of adaption and of disturbed homoeostasis.' According to this theory, homoeostasis is achieved by adaption to a pharmacologic agent and can be disturbed by contraregulatory mechanisms when the agent is withdrawn. This hypothesis has been supported by several findings in electrophysiology. For instance, Ritter and Duensing (1970) found in 30 alcoholics that there was an unequivocal disinhibition in the function of polysynaptic reflexes prior to the alcoholic delirium.

These observations add to the clinical symptomatology of the delirium which besides disorientation and hallucinations is characterized by gross psychomotor excitation. Symptomatology in conjunction with physiologic findings suggest that the catecholamines and their metabolites which can be measured in body fluids such as blood, cerebrospinal fluid (CSF) and urine may reflect the hyperactivity in the central noradrenergic and dopaminergic nervous system.

Giacobini and his associates (1960) found that noradrenaline (NA) and adrenaline (A) were excreted in high amounts during the alcoholic delirium. These were clearly higher than in alcoholic intoxication or during the usual withdrawal symptoms. The peak of the A and NA excretion was correlated with the intensity of clinical symptomatology. Increased excretion of A and NA disappeared after 3 to 9 days after the end of delirium.

The purpose of this study was to investigate whether there are changes of the metabolites of NA and dopamine (DA), i.e., 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA) in the CSF during the alcoholic delirium and a drug free control period. In addition, urinary DA, A, and NA excretion and the activity of dopamine-β-hydroxylase (DBH) in serum were measured at identical times.

Methods

Eight male patients with an alcoholic delirium were studied in the Psychiatric Hospital of the University of Munich. Patients with a serious somatic disease, head injuries or known other psychiatric illnesses prior to the alcoholism were excluded from the study. All patients were

Table 1. Delirium tremens rating scale

1. Consciousness: clear = 0, clouded = 1, somnolent = 2, unconscious = 3
2. Oriented to person: yes = 0, no = 3
3. Oriented to year: yes = 0, no = 3
4. Oriented to month: yes = 0, no = 3
5. Oriented to day or date of the month: yes = 0, no = 1
6. Oriented to place (town): yes = 0, no = 3
7. Oriented to place (hospital, psychiatric hospital): yes = 0, no = 3
8. Understands his situation: yes = 0, no = 3
9. Visual hallucinations: no = 0, questionable = 1, yes = 2
10. Auditory hallucinations: no = 0, questionable = 1, yes = 2
11. Short term memory: as described under [a]
12. Feelings of one's actions being influenced: no = 0, questionable = 1, yes = 2
13. Suggestibility: no = 0, yes = 3
14. Anxiety: no = 0, mild = 1, moderate = 2, marked = 3
15. Motor agitation, picking hand movements: no = 0, mild = 1, moderate = 2, marked = 3
16. Tremor: no = 0, mild = 1, moderate = 2, marked = 3
17. Heightened superficial reflexes: no = 0, present = 1, marked = 2
18. Tremulous tongue, lips or face-trembling: no = 0, present = 1, marked = 2
19. Shaking: no = 0, present = 1, marked = 2
20. Sweating: no = 0, present = 1, marked = 2
21. Nausea: no = 0, yes = 1
22. Vomiting: no = 0, yes = 1

[a] Ask for longest series of numbers the patient is able to recall. Scoring: 7 numbers = 0, 5 numbers = 1, 3 numbers = 2.0, 2 numbers = 2.5

drug free for at least two weeks prior to the hospitalization. The beginning of the delirium tremens had to be within the 5 h preceding the investigation.

Routine laboratory checks were performed in the beginning of the study.

Ages of the patients were between 30 and 62 years (mean 40.5 years).

Diagnoses were established by two experienced psychiatrists on the basis of an assured alcoholic anamnesis when disorientation, visual hallucinations and tremor were present. Disorientation and hallucinations were the criteria for defining the beginning and the end of the delirium tremens.

A special rating scale was used (Table 1) where each clinical variable was expressed by a number which indicates the weight of its presence for establishing the diagnosis. Addition of these scores yielded an individual global clinical rating score for each patient in regard to intensity and duration of the delirium. Clinical ratings took place every 6 h starting at the beginning of the study and lasting until 24 h after the delirium was terminated.

Collection of blood, urine and CSF samples was performed according to a fixed schedule which is depicted in Table 2:

Period A signifies the beginning of the study (patient without any medication).

Period B/C/D signifies the three consecutive days during the delirium.

The control period took place after at least 15 days or later, provided that the patient was without any medication for at least 10 days.

Period E/F/G signifies the three consecutive days at the beginning of the control period.

Urine was taken at period A if possible. During all other periods 24-h collections were performed (0700 to 0700). Urine was stored cool under addition of sodium metabisulfite and then frozen and kept at $-40°C$ until analysis was done.

Table 2. Schematic view of the different study phases, during which collections of the different body fluids were performed. Number of patients and course of the chlormethiazol treatment are indicated

Periods[a]		A	B	C	D	interval	E	F	G
Urine[b]	— dopamine	+	+	+	+		+	+	+
	— noradrenaline	+	+	+	+		+	+	+
	— adrenaline	+	+	+	+		+	+	+
Serum[c]	— DBH	+	+	+	−		+	+	+
CSF[d]	— MHPG	+	−	−	−		+	−	−
	— HVA	+	−	−	−		+	−	−
Chlormethiazol treatment		−	+	+	+		−	−	−
Number of patients in delirium		9	7	4	2		−	−	−

Comments:

[a] period A: first day of admittance of the patient into the study; period B, C, D: 2nd to 4th consecutive days after admittance of the patient into the study; period E, F, G: control period. 3 consecutive days after the end of the delirium and at least 10 days without any medication

[b] urine: collection of the first voiding *before* medication (period A); 24 hours urine collections through period B—G

[c] serum: in period A before medication; in period B, C, and E—G taken at 0800 before breakfast

[d] cerebrospinal fluid: lumbar puncture in a sitting position; during period A at irregular times of the day; during period G at 0800 before breakfast

Blood was taken by venupuncture into Heparin-Monovetten (Sarstedt), centrifuged and kept frozen at −40°C until analysis.

The first lumbar puncture was performed in period A in a sitting position, the second one was performed during the beginning of the control period at 0800. CSF collection was done according to a fixed fraction schedule: the first 3 ml for routine laboratory checks, 4 ml for HVA and 4 ml for MHPG estimation. CSF was collected without any preservative and immediately frozen to −20°C.

The biochemical estimations of DA, NA, and A in urine were performed according to a modified method of Weil-Malherbe (1971). Activity of DBH in serum was estimated according to a method of Markianos and Nyström (1975). MHPG was measured according to the method of Dekirmenjian and Maas (1970). HVA was measured by gas chromatography using an electrone capture detector (Markianos and Beckmann, 1976).

In addition blood pressure, body temperature and pulse rate were measured hourly during the delirium and twice daily during the control period.

Chlormethiazol was used for the treatment of the delirium after the period A, in doses of 3.5—10 g/day, average 6.1 g. Statistical tests were done by Student's *t*-test for paired and grouped data and Pearson's *r*.

Results

Clinical Findings

Duration of the delirious states ranged from 14 to 240 h (average 62 h). Maximum intensity of the delirium was present already in the beginning of the study (Period A) in 7 patients, whereas two patients showed highest intensity 18—24 h

after the initial phase. Blood pressure did not show any substantial changes during the delirium as compared to the control period (mean 135/85 : 125/80). Pulse rate was only insignificantly elevated during the delirium in comparison to the control period (104 : 96). Body temperature was elevated in all patients over 38°C during the delirium. Inspection of the routine laboratory data revealed moderate anemia in most of the patients (10.0—15.2 g%, mean 13.2 g%), slightly increased bilirubin (mean 1.35 mg%; normal 0.2—1.1 mg%), elevated transaminases (GOT 54, normal < 18; GPT 57, normal < 22) and reduced potassium levels (mean 3.3 mval/l, normal 3.8—5.0 mval/l).

NA, A, DA in Urine

Urinary NA excretion was significantly elevated during the delirium as compared to the control period (period A versus period E): 6.08 ± 2.3 versus 2.28 ± 0.97 ng/0.1 g creatinine ($P < 0.01$ Student's t-test). NA excretion showed decreasing values during periods B through D under the medication of chlormethiazol (Fig. 1).

Similar findings were obtained by measuring the A excretion during the delirium and the control period (2.41 ± 0.33 in period A versus 0.90 ± 0.48 ng/0.1 g creatinine in period E). This difference is statistically significant ($P < 0.02$ Student's paired t-test).

Consecutive excretion values for NA, A and DA for all periods are graphically depicted in Figure 2.

As can be seen from this figure DA excretion was elevated only during period A as compared to the consecutive periods B, C, D (23.6 ± 10.9 versus 15.9 ± 6.7 ng/0.1 g creatinine; $P < 0.02$ Student's paired t-test). The complete DA

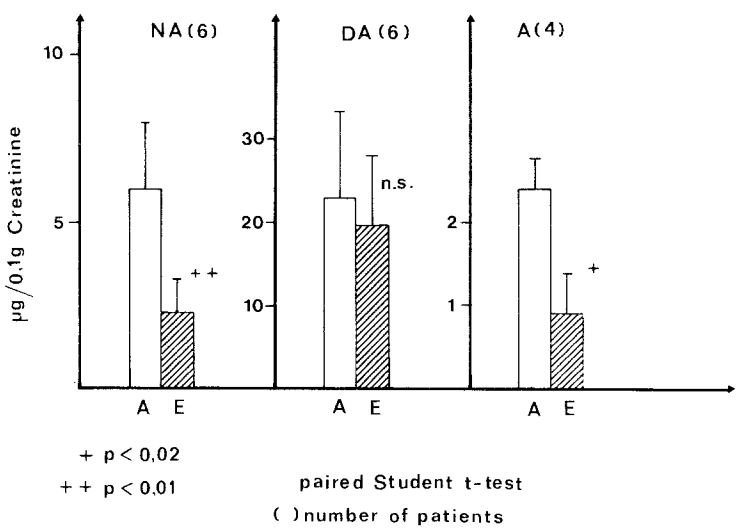

Fig. 1. Average values of the catecholamines noradrenaline (NA), dopamine (DA) and adrenaline (A) excreted in urine during the delirium (unmedicated phase period A) and the drug free control day (period E)

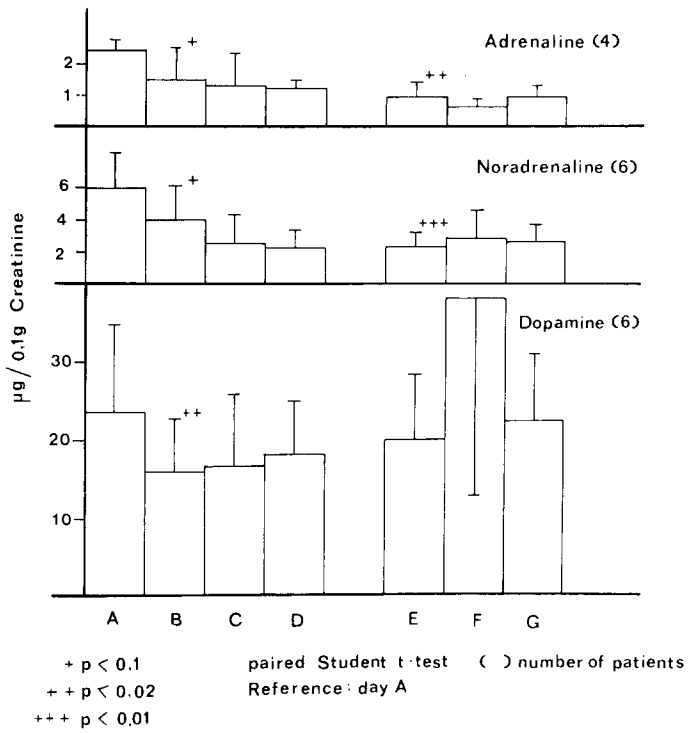

Fig. 2. Urinary excretion of the catecholamines during delirium and consecutive days (period A through D) and during the control period (period E through G). For explanation of the different study periods see Table 2

Table 3. DBH activity in nmol/ml serum/h in eight patients (nine delirious states). Body fluids which were collected during the delirium are indicated by '*'

Patient	A	B	C	E	F	G
1	143.9*	144.0*	155.5*	131.1	131.8	146.6
2	150.5*	138.1*	149.5	143.5	139.0	133.1
3	52.2*	38.3*	34.9*	21.9	21.9	29.1
3a	44.8*	45.0*	30.2	27.5	24.6	24.6
4	128.9*	114.7	131.4	128.9	130.0	127.2
5	89.4*	98.1*	88.1	62.9	72.4	60.3
6	124.3*	119.0*	125.0*	102.2	93.1	95.9
7	39.6*	42.3	34.5	33.3	37.6	38.7
8	78.7*	68.4*	66.8*	45.6	48.6	41.2
Average values						
$n=9$	94.7 ± 43.6	89.7 ± 42.1	90.6 ± 51.2	77.4 ± 49.1	77.7 ± 47.5	77.4 ± 48.6
$n=8$	100.93 ± 42.08			83.67 ± 48.47		
Statistical significance (Student's t-test for paired data)						
	$P<$ ref.	n.s.	n.s.	0.002	0.002	0.002

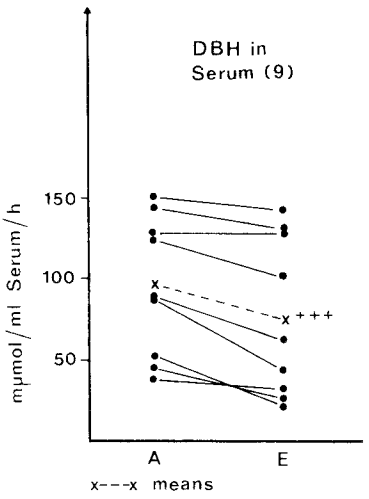

Fig. 3. DBH-activity in the sera of the individual patients during the delirium (A) and the control period (E). *** $P<0.002$ student's t-test

excretion during the delirium was not significantly elevated for the patients as a group when compared to the control period.

DBH in Serum

In serum DHB was elevated during the entire delirious state when compared with the drug free period, and there is a remarkable constancy from period to period in the delirium and the control period as well (Table 3). Comparing the DBH activity in serum from period A to period E (94.7 ± 43.6 versus 77.4 ± 49.1 nmol/ml serum/h; $P< 0.002$ Student's paired t-test) it becomes evident that there is a significant elevation of DBH activity during the delirium also in every individual patient except one (Fig.3).

Plotting the intensity of the alcoholic delirium (as represented by the maximum scores on the delirium rating scale) and the activity of DBH in serum by linear regression analysis, a statistically significant correlation can be found ($r=0.64$; $P<0.05$; Fig. 4).

MHPG and HVA in CSF

As can be seen from Figure 5, the mean MHPG concentration in cerebrospinal fluid during the unmedicated delirium phase was 25.5 ± 9.1 ng/ml and during the control period 10.7 ± 6.5 ng/ml in all studied patients. This difference is significant ($P<0.001$ Student's paired t-test). It is noteworthy that there was no exception in the individual patients, i.e., every patient showed a higher MHPG concentration during the delirium as compared to the control period.

Conversely, HVA showed an average level of 46.3 ± 19.5 ng/ml during the delirium and 57.1 ± 35.2 ng/ml during the control period. This difference is not statistically significant.

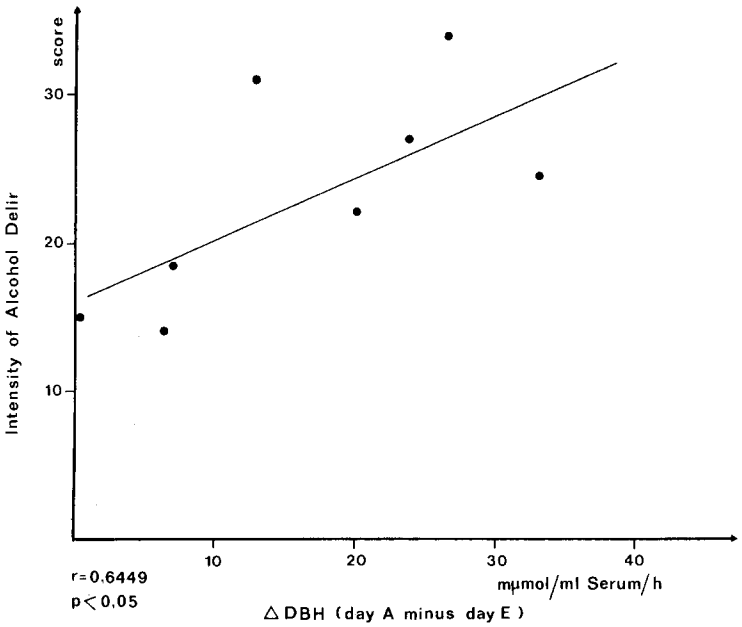

Fig. 4. Correlation between the intensity of alcoholic delirium (as measured on the delirium tremens rating scale) and the DBH-activity in the sera of the patients by linear regression analysis

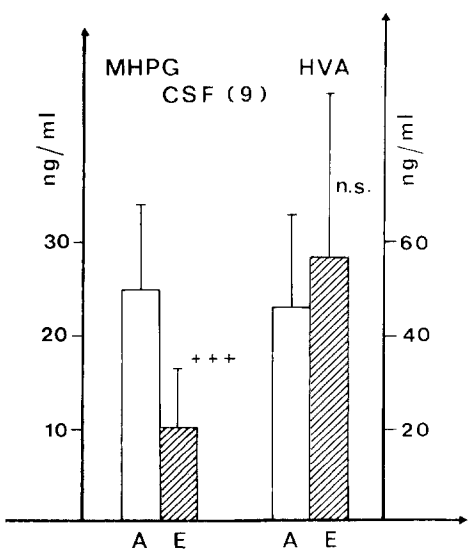

Fig. 5. Average concentrations of MHPG and HVA in cerebrospinal fluid of the patients as a group during delirium (period A) and a control day (period E). *** $P < 0.001$ Student's t-test

Longitudinal Study of One Patient with Two Deliriums Within 4 Months

One of our patients had to be treated twice for delirium within 4 months. The biochemical data of the two pathologic states is shown in Table 4. As can be seen,

Table 4. Investigation of two consecutive deliriums in the same patient within 4 months. Urine was not collected during second delirium

		1st delirium Period		Discharge	2nd delirium Period	
		A 1	E 1		A 2	E 2
Days		0	30	40	105	125
Urine:	DA	17.7	13.0		—	—
	NA	8.8	3.06		—	—
	A	2.28	0.65		—	—
Serum:	DBH	52.2	21.9		44.8	27.5
CSF:	MHPG	17.0	12.0		18.5	7.5
	HVA	54.4	88.2		23.5	58.9
Intensity of delirium (total score)		29	—		24.5	—
Duration of delirium (hours)		67	—		21.0	—

the same relationships between the data of the delirium and the control period were presented in the two study phases. Both MHPG and DBH were consistently higher during the delirium as compared to the control period. Urine collections could not exactly be performed during the second delirium. In this single patient HVA was significantly lower during the psychotic phase as compared to the control period.

Discussion

There seems to exist some evidence that the alcoholic delirium is a psychopathologic state at the end of a progressing withdrawal syndrome. The basic mechanism is thought to be the psychomotor excitation which is expressed in its slightest manifestation by tremor and later by hallucinations and disorientation (Johnson, 1961). Gross and his associates agree on this; however, they stress that the progression in the withdrawal syndrome seems to be more saltatoric than linear (1974). This is also confirmed by the investigation of Feuerlein (1972). Therefore it appears to be justified to compare some of the biochemical findings in alcoholic withdrawal syndrome with those obtained during manifest delirium.

Our findings of a significantly elevated urinary excretion of NA during delirium is consistent with those of Giacobini et al. (1960) and Mendelson et al. (1969). Ogata and his associates (1971) found also an increase of urinary excretion of catecholamines and their metabolites during chronic ethanol ingestion, and this increase was even more intensified after withdrawal from alcohol.

Excretion of the catecholamines was not affected after ingestion of a single dose of ethanol in the same study. This is in agreement with data from various

animal studies, where increases of both NA turnover and NA release were found (Ahtee and Svartström-Fraser, 1975; Pohorecky, 1974; Hunt and Majchrowicz, 1974). Similarly an increased plasma level of noradrenaline was demonstrated during abstinence syndrome by Carlsson and Häggendahl (1967).

It is remarkable that the activity of DHB in serum parallels the increase of catecholamine excretion. This enzyme has been investigated in patients with various diseases, including torsion dystonia (where it is increased, Wooten et al., 1973) and familial dysautonomia and mongolism (where it is decreased, Freedman and Goldstein, 1974; Weinshilboum and Axelrod, 1971). In addition, an enhancement was found after maximum work load (Planz and Palm, 1973), and it is thought that DBH activity may reflect the tone of the sympathetic nervous system. Inspection of the individual data reveals that all patients (except patient No. 4) showed an elevated DBH activity during the delirium as compared to the control period. Of special interest is the positive correlation between the height of of the DBH activity in serum and the intensity of the alcoholic delirium, as measured on the delirium tremens rating scale. From this it may be concluded that there is a correlation between the increased sympathetic activity and alcoholic delirium provided that one can conclude from peripheral to central noradrenergic activity.

MHPG which best may reflect the central noradrenergic metabolism was elevated 137% in comparison to the control period in CSF. In this regard the findings of Ogota et al. (1971), who found a significant decrease in urinary VMA excretion and a concomitant increased MHPG excretion during the alcoholic withdrawal syndrome, are of interest. Because of this, a shift from metabolic oxidation to reduction in the final pathway of noradrenaline metabolism is indicated. In CSF of healthy control persons the MHPG : VMA ratio is very high (Jimerson et al., 1975). Therefore it seems not to be conceivable that the increase of MHPG concentration in lumbar CSF is exclusively due to a metabolic shift from oxidation to reduction. Rather it may be considered an indicator of strong *central* noradrenergic hyperactivity during alcoholic withdrawal syndrom, i.e., delirium.

The urinary excretion of A parallels the findings with NA excretion with a broader interindividual variation. Nevertheless, the patients as a group, showed a clearly significant elevation during the delirium as compared to the control period. This is in agreement with the findings of other investigators (Giacobini et al., 1960; Carlsson and Häggendal, 1967).

Estimation of urinary DA excretion was difficult in that there were large interindividual variations both in the delirium and the control period. In addition, there were large intraindividual variations from day to day without any correlation with clinical variables, such as height of blood pressure, pulse rate and body temperature. There was no significant alteration in urinary DA excretion in the patients as a group; this is in line with various findings of other investigators (Ogota et al., 1971) and is consistent with pharmacological studies in brains of laboratory animals (Ahtee and Svartström-Frazer, 1975), though not all studies agree (Griffith et al., 1974; Hunt and Majchrowicz, 1974).

HVA in CSF, which best may reflect the activity of the central dopaminergic system did not show a significant elevation during the delirium as compared to

the control period. Rather there was a slight and insignificant reduction of HVA during the withdrawal syndrome. This is in line with the results obtained by Roos and his associates (1973) who also found *low* values during abstinence syndrome in patients suffering from chronic alcoholic ataxia as well. Again, this is in agreement with laboratory studies in alcohol dependent rats, which did not show any alteration of HVA concentration in the brains of the animals (Ahtee and Svartström-Frazer, 1975).

It remains somewhat problematical whether or not the increased central and peripheral noradrenergic activity may be more state dependent, i.e., due to the concomitant stress and the psychomotor activity during the disease. It has long been known that increase in psychic stress, physical activity and changes in posture all affect the excretion of urinary catecholamines and their metabolites (Euler, 1971; Karki, 1956; Sudin, 1958) and the level of MHPG in CSF (Ebert et al., 1973), though not all studies agree (Goode et al., 1973).

However, it has been shown by Post and Goodwin (1973) that simulation of mania and increased physical activity lead to an increase of all *three* metabolites in CSF, i.e., HVA, 5-HIAA and MHPG. Conversely, in this study only MHPG was elevated. Thus it can be hypothesized that hyperactivity of the central and peripheral noradrenergic system as expressed in the increase of catecholamine excretion, DBH activity in serum and MHPG in CSF might be of significance for the alcoholic withdrawal syndrome.

The increased activity of the noradrenergic system may have a protective function in ethanol withdrawal. By inhibiting the synthesis of catecholamines by α-methyl-p-tyrosine (αMPT) withdrawal symptoms were aggravated in mice (Blum and Wallace, 1974; Griffiths et al., 1974; Goldstein, 1973). In addition, Collier et al. (1974) showed that the injection of NA into the cerebral ventricles as well as amphetamine administration markedly inhibited ethanol withdrawal head twitches in mice. Further animal and human studies should be done to clarify the significance of the noradrenergic hyperactivity in order to get a more specific treatment for the ethanol withdrawal syndrome, particularly delirium tremens.

References

Ahtee, L., Svartström-Frazer, M.: Effect of ethanol dependence and withdrawal on the catecholamines in rat brain and heart. Acta pharmacol. et toxicol. **36**, 289—298 (1975)

Blum, K., Wallace, I. E.: Effects of catecholamine synthesis inhibition on ethanol-induced withdrawal symptoms in mice. Br. J. Pharmac. **51**, 109—111 (1974)

Carlsson, C., Häggendal, J.: Arterial noradrenaline levels after ethanol withdrawal. Lancet **1967II**, 889

Dekirmenjian, H., Maas, J. W.: An improved procedure of 3-methoxy-4-hydroxcyphenylethyleneglycol determination by gasliquid chromatography. Anal. Biochem. **35**, 113—122 (1970)

Ebert, M. H., Post, R. M., Goodwin, F. K.: Effect of physical activity on urinary MHPG excretion in depressed patients. Lancet **130**, 67—72 (1973)

Euler, O. S. v.: Adrenergic transmitter functions. Science **172**, 202—206 (1971)

Feuerlein, W.: Zur Frage des Alkohol-Entzugssyndroms. Der Nervenarzt **43**, 247—253 (1972)

Freedman, L. S., Goldstein, M.: Serum-beta-hydroxylase in Down's syndrome: A familial study. Res. Comm. Chem. Pharmac. **8**, 543—549 (1974)

Giacobini, E., Izikowitz, S., Wegmann, A.: Urinary norepinephrine and epinephrine excretion in delirium tremens. Arch. gen. Psychiat. **3**, 289—296 (1960)

Goldstein, D. B.: Alcohol withdrawal reactions in mice: Effects of drugs that modify neurotransmission. J. Pharmacol. Exp. Therap. **186**, 1—9 (1973)
Goode, D. J., Dekirmenjian, H., Meltzer, H. Y., Maas, J. W.: Relation of exercise to MHPG excretion in normal subjects. Arch. Gen. Psychiat. **29**, 391—396 (1973)
Griffith, P. J., Littleton, J. M., Ortiz, A.: Changes in monoamine concentrations in mouse brain associated with ethanol dependence and withdrawal. Br. J. Pharmac. **50**, 489—498 (1974)
Gross, M. M., Lewis, E., Hastey, J.: Acute alcohol withdrawal syndrome. In: Kissin, B. and H. Begleiter (Eds.): The Biology of Alcoholism. Vol. III. New York-London: Plenum Press 1974
Hunt, W. A., Majchrowicz, E.: Alterations in the turnover of brain norepinephrine and dopamine in alcohol-dependent rats. J. Neurochem. **23**, 549—552 (1974)
Jimerson, D., Gordon, E. K., Post, R. M., Goodwin, F. K.: Central norepinephrine function in man: VMA in the CSF. Sci. Proc. Am. Psych. Ass. **128**, 94—96 (1975)
Johnson, R. B.: The alcohol withdrawal syndromes. Quart. J. Stud. Alcohol Suppl. **1**, 66—76 (1961)
Kalant, H.: The pharmacology of alcohol intoxication. Quart. J. Stud. Alcohol Suppl. **1**, 1—23 (1961)
Karki, N. T.: The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variations and the effect of muscular work on it. Acta Physiol. Scand. Suppl. **132**, 1—96 (1956)
Maas, J. W., Dekirmenjian, H., Garver, D., Redmond, D. E., Jr., Landis, D. H.: Excretion of catecholamine metabolites following intraventricular injection of 6-hydroxydopamine in the macaca speciosa. Europ. J. Pharmacol. **23**, 121—130 (1973)
Markianos, E. S., Nyström, I.: Serum dopamine-β-hydroxylase. Z. Klin. Chem. Klin. Biochem. **13**, 273—276 (1975)
Markianos, E. S., Beckmann, H.: Diurnal changes in dopamine-β-hydroxylase, homovanillic acid and 3-methoxy-4-hydroxyphenylglycol in serum of man. J. Neur. Transm. **39**, 79—93
Ogata, M., Mendelson, J. H., Mello, N. K., Majchrowicz, E.: Adrenal function and alcoholism: II. Catecholamines. Psychosom. Med. **33**, 159—180 (1971)
Planz, G., Palm, D.: Acute enhancement of dopamine-β-hydroxylase activity in human plasma after maximum work load. Europ. J. Clin. Pharmacol. **5**, 255—258 (1973)
Pohorecky, L. A.: Effects of ethanol on central and peripheral noradrenergic neurons. J. Pharmac. Exp. Therap. **189**, 380—391 (1974)
Post, R. M., Goodwin, F. K.: Simulated behaviour states. Biological Psychiatry **7**, 237—254 (1973)
Ritter, G., Duensing, F.: Exterozeptive Reflexenthemmung beim Delirium tremens. Der Nervenarzt **41**, 439—444 (1970)
Roos, B. E., Silfverskiöld, B. P.: Homovanillic acid in cerebrospinal fluid of alcoholics. The New England Journal of Medicine 1358 (1953)
Sudin, T.: The effect of body posture on the urinary excretion of adrenaline and noradrenaline. Acta Med. Scand. **161**, Suppl. 336 (1958)
Weil-Malherbe, H.: Analysis of biogenic amines and their related enzymes. In: Methods of Biochemical Analysis. David Glick (Ed.) New York: John Wiley & Sons 1971
Weinshilboum, R. M., Axelrod, J.: Reduced plasma dopamine-beta-hydroxylase activity in familial dysautonomia. N. Eng. J. Med. **285**, 928—942 (1971)
Wieser, S.: Alkoholismus II: Psychiatrische und neurologische Komplikationen. Fortschr. Neurol. Psychiat. **33**, 349—409 (1965)
Wooten, F. G., Eldridge, R., Axelrod, J., Stern, R. S.: Elevated plasma dopamine-beta-hydroxylase in autosomal dominant torsion dystonia. N. Eng. J. Med. **288**, 284—287 (1973)

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