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Sleep patterns in congenital dopamine beta-hydroxylase deficiency

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Summary. Sleep patterns of two young female patients with congenital dopamine beta-hydroxylase deficiency are described. In this orthostatic syndrome central and peripheral noradrenergic failure occurs as a result of impaired beta-hydroxylation of dopamine. Consequently, the levels of dopamine and its metabolites are elevated. The relative importance of noradrenaline deficit in the face of dopamine excess for sleep-regulatory mechanisms can be inferred from the sleep pattern of these patients. No subjective sleep complaints were reported. The sleep patterns showed a high percentage of slow-wave sleep in both patients (29% and 34% of sleep period time) and a relatively low to normal percentage of REM sleep (18% and 21%). A normal cyclic REM sleep pattern was observed. Alpha-delta sleep occurred during light sleep (15% and 8%); consequently, the amount of stage 2 sleep was reduced. These results indicate that functional insufficiency of the noradrenergic system in two patients with dopamine beta-hydroxylase deficiency is not associated with profound changes in the (REM) sleep pattern. This supports a modulatory or permissive role for noradrenaline in REM sleep mechanisms.

Key words: Noradrenaline – Dopamine – Sleep – REM sleep – Dopamine beta-hydroxylase deficiency

Introduction

Numerous attempts have been made to relate the role of neurotransmitters, especially noradrenaline, serotonin, dopamine and acetylcholine, to the different stages of sleep (for reviews, see [1, 7, 23]). Currently, it is clear that a number of biochemical and neuronal events are involved in the induction of different sleep states and that no single neurotransmitter is solely responsible for one distinct function.

The role of neurotransmitters in the initiation and maintenance of sleep, as well as the induction of rapid eye movement (REM) and non-REM (NREM) sleep, have been studied in man primarily by pharmacological methods. Distinct from this pharmacological approach, the syndrome of congenital dopamine beta-hydroxylase (DBH) deficiency, as an experiment of nature, may serve to illustrate the relative importance of some of these neurotransmitters.

Sleep characteristics of two patients with selective noradrenergic failure as a result of a DBH deficiency, both centrally and peripherally, were studied. In this syndrome excessive amounts of dopamine and its metabolites were found in plasma, urine and cerebrospinal fluid (CSF), whereas noradrenaline, adrenaline and their metabolites could not be detected. The relative importance of noradrenaline and dopamine in sleep-wake regulatory mechanisms can be inferred from the study of the sleep pattern of these patients.

Patients and methods

The two female patients have been described in detail elsewhere [11, 13]. They were 31 and 21 years of age. Both patients presented with severe orthostatic hypotension, which appeared to be due to autonomic failure, since the phase IV in the Valsalva response was absent. Autonomic failure was due to selective noradrenergic failure as a result of DBH deficiency. The defect could be demonstrated both centrally and peripherally; noradrenaline and adrenaline were undetectable in plasma, urine and CSF, but dopamine was 7- to 12-fold increased in plasma, 4-fold in urine, and 20-fold in CSF. Normetanephrine, metanephrine, 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) and vanillylmandelic acid were not detectable in urine and MHPG was also not detectable in CSF, which was further evidence for impaired beta-hydroxylation of dopamine. Accumulation of dopamine was also shown by increased levels of its metabolites; homovanillic acid (HVA) and 3-methoxytyramine were elevated in urine and HVA was also elevated in CSF. Indeed, DBH activity could not be detected in plasma or CSF. A summary of the biochemical findings of these patients is given in Table 1.

Cholinergic function (sweating, heart rate, gastric acid production, pupil diameter) was intact. Physiological and pharmacological manoeuvres to manipulate sympathetic neurotransmitter release (hypoglycaemia, ganglionic stimulation, tyramine, head-up tilting, yohimbine, clonidine) caused changes in dopamine, whereas noradrenaline and adrenaline were never detected. These data suggest that in the syndrome of congenital DBH deficiency dopamine rather than noradrenaline is released as the sympathetic neurotransmitter, but that the sympathetic neuron is otherwise intact [12, 13].

Blood pressure. Twenty-four-hour blood pressure profiles were recorded in the two patients by means of the Oxford technique,

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Table 1. Biochemical data of two patients with autonomic failure due to dopamine beta-hydroxylase deficiency, as compared with other patients with chronic autonomic failure due to various causes

Tests	DBH deficiency	Chronic autonomic failure	Normals
	($n = 2$)	($n = 12$)	($n = 56$)
Plasma noradrenaline (nmol/l)	0	0.5, 0.1	1.8, 1.0
Plasma adrenaline (nmol/l)	0	0.25, 0.19	0.40, 0.30
Plasma dopamine (nmol/l)	3.4, 0.3	0.50, 0.21	0.43, 0.28
	($n = 2$)	($n = 9$)	($n = 20$)
Urinary VMA (μmol/mol creatinine)	0	400, 310	1600, 520
Urinary MHPG (μmol/mol creatinine)	0	550, 210	1120, 430
Urinary HVA (μmol/mol creatinine)	5400, 200	640, 490	2050, 780
	($n = 1$)	($n = 0$)	($n = 12$)
Cerebrospinal fluid noradrenaline (nmol/l)	0	–	0.6, 0.3
Cerebrospinal fluid adrenaline (nmol/l)	0	–	0.06, 0.03
Cerebrospinal fluid dopamine (nmol/l)	1.8	–	0.1, 0.1
Cerebrospinal fluid MHPG (nmol/l)	0	–	55, 18
Cerebrospinal fluid HVA (nmol/l)	580	–	280, 160

Data were taken from [11, 13]. Indicated are means, SD. DBH = Dopamine beta-hydroxylase; VMA = free vanillylmandelic acid; MHPG = 3-methoxy-4-hydroxyphenylethylene glycol; HVA = homovanillic acid

which has been described in detail elsewhere [14]. The 24-h blood pressure profiles and sleep records were made on separate occasions. One patient had not taken drugs for her orthostatic hypotension for 3 months, whereas in the other patient pindolol (5 mg od) was stopped 2 weeks before the recordings.

Sleep recordings and analyses. The sleep recordings were made in the clinic: four consecutive recordings of patient 1 and three recordings of patient 2. Bed-time and rise-time were scheduled for each patient to approximate home sleep patterns.

All night polysomnographic recordings included two electrooculograms (EOGs), two EEG derivations (C3–A2; C4–A1) and submental chin EMG, according to standardized lead placements [16], in addition to frontal, temporal and occipital EEG leads (F4–C4, C4–P4, P4–O2, F3–C3, C3–P3, P3–O1, T4–C0, C0–T3). All signals were amplified and monitored on a 21-channel Siemens Elema electroencephalograph. An amplification of 50 μV/cm was used in the EEG channels and 100 μV/cm in the EOG channels. The time constants for the EOG and EEG recordings were 1.2 s and the high frequency cut-off was 70 Hz. For the EMG we used a time constant of 0.015 s and a high frequency cut-off of 300 Hz.

Sleep stages were defined (in 30-s epochs) according to the criteria of Rechtschaffen and Kales [16] by two independent researchers. Sleep parameters were calculated according to the definitions of Williams et al. [24]. Alpha-delta sleep occurred in both patients. This pattern consisted of the intrusion of the EEG alpha frequency into NREM sleep as well as of the regular occurrence of 10–20 s of alpha-like activity, alternating with delta bursts. This sleep characteristic was quantified separately by counting the number of 30-s epochs with a predominance of alpha-delta sleep (i.e. if more than 50% of the epoch consisted of this EEG pattern). In addition, spindles were measured for frequency of occurrence according to the following criteria: the wave form should have a duration of at least 0.5 s, a frequency of 12–16 Hz and a peak amplitude of at least 20 μV. The sleep data of our patients were compared with normal values from the literature for age- and sex-matched controls [20, 24] which have been assembled by means of similar research procedures to our own. The data on females (20–29 years) reported by Williams et al. [24] were considered to be representative for healthy female controls.

The first night in the clinic was the adaptation night. The data of all other nights are presented.

Results

The diurnal blood pressure profile is reversed in these patients, so that they have the highest pressures early during the night and the lowest pressures early during day-time ambulation (Fig. 1). As a consequence, patients with chronic autonomic failure show the phenomenon known as "pressure-natriuresis", which is responsible for patients waking up during the night when they have to void urine [10, 19].

No subjective sleep complaints were reported by either patient, although a general feeling of fatigue was present especially in the morning, which is typical for patients with severe orthostatic hypotension. Early in the morning after rising from bed, blood pressure dropped to such a low level that it was not possible for the

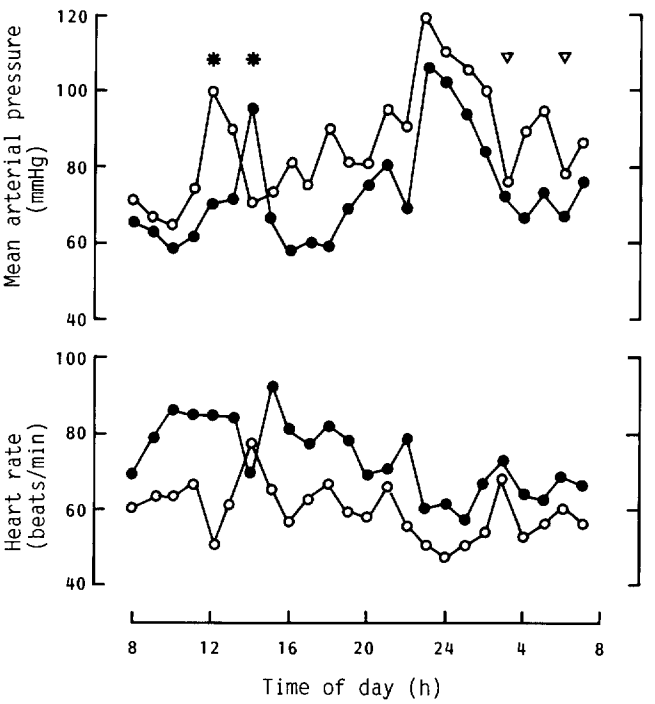

Fig. 1. Diurnal blood pressure and heart rate patterns in two patients with dopamine beta-hydroxylase deficiency. Indicated are hourly averages of integrated mean arterial pressure. ●, Patient 1; ○, patient 2; ∗, diners, sitting in bed, followed by postprandial hypotension; ▽, left bed to void urine. Sleep period from 2200 to 0700 hours. Note the reversal of the diurnal blood pressure rhythm, but the normal diurnal rhythm of heart rate

Table 2. Sleep parameters of all nights per patient. Control data of ten women (20–29 years) were obtained from Williams et al. [24]

Sleep parameters		Patient 1 Night			Patient 2 Night		Control (10 women)	
		2	3	4	2	3	Mean	SD
Time in bed (min)		496.0	497.5	411.5	459.5	470.0	445.7	24.0
Sleep period time (min)		460.0	436.5	390.5	453.5	468.0	432.3	22.0
Total sleep time (min)		458.5	436.5	380.5	448.0	435.5	429.9	21.7
Time awake (W) (min)		1.5	0.0	10.0	5.5	32.5		
Movement time (MT) (min)		3.5	1.5	5.0	6.0	5.0		
Sleep latency (min)		5.5	21.5	11.0	6.0	4.5	12.9	9.6
Sleep efficiency index		0.92	0.88	0.92	0.97	0.93	0.96	0.02
Minutes of stage	1	32.5	28.0	15.0	14.5	15.5		
	2	145.5	128.5	66.5	151.5	154.5		
	3	38.0	38.5	63.5	64.5	47.5		
	4	112.5	95.0	85.5	86.0	71.5		
	REM	76.0	83.0	71.5	90.5	105.0		
	Alpha-delta	50.5	62.0	73.5	35.0	36.5		
% of stage	W	0.3	0.0	2.6	1.2	6.9	0.5	0.5
	1	7.1	6.4	3.8	3.2	3.3	4.2	2.4
	2	31.6	29.4	17.0	33.4	33.0	52.4	5.9
	3	8.3	8.8	16.3	14.2	10.2	5.3	2.0
	4	24.5	21.8	21.9	18.9	15.3	12.4	6.2
	Slow wave sleep (3 + 4)	32.8	30.6	38.2	33.1	25.5	17.7	6.7
	REM	16.5	19.0	18.3	20.0	22.4	25.2	3.6
	Alpha-delta	11.0	14.2	18.8	7.7	7.8		
	MT	0.8	0.3	1.3	1.3	1.1		
REM latency (min)		131.0	116.5	98.0	120.0	117.0	100.2	44.2
Number of REM periods		3	4	4	5	5	4.2	0.9
REM period length (min)	$\bar{X}$	23.0	20.8	19.8	17.9	21.0	28.0	3.9
	SD	25.2	4.6	4.4	10.7	16.2		
NREM/REM cycle length (min)	$\bar{X}$	153.0	98.5	97.4	89.7	89.7	115.6	48.1
	SD	46.2	30.7	17.5	47.0	34.8		

patients to walk more than a few metres without sitting down (Fig. 1). Orthostatic hypotension made it impossible for the patients to participate in active physical activities. This was especially true for patient 1. Post-lunch naps occasionally occurred in patient 1, also during this study. These naps coincided with drops in blood pressure such as is normally observed shortly after meals in patients with chronic autonomic failure (Fig. 1).

Sleep characteristics

Sleep started soon after "lights out" in both patients; sleep latency was within normal limits (Table 2). Sleep was continuous and undisturbed for the whole sleep period in patient 1. Patient 2 woke up for a short period in one of the two nights, during which she needed to go to the toilet to void urine. After returning to bed, sleep was resumed almost instantly. Sleep stage percentages indicated the presence of a high percentage of slow-wave sleep (SWS) (stages 3 + 4) (patient 1: 34%; patient 2: 29%), caused by an increased amount of both stage 3 and stage 4 sleep. Healthy young adults are reported to spend ± 20% of their sleep time in SWS [24] (Table 2). A relatively low to normal percentage of REM sleep (patient 1: 18%; patient 2: 21%) was observed, compared with the 25% of REM sleep normally found in young adults [24]. REM latency was within normal limits, as was the cyclic occurrence of the REM periods (Fig. 2). The occurrence of alpha-delta sleep (Fig. 3) was more explicit in patient 1 than in patient 2: 15% and 8%. The alpha rhythms were in the 7–10 Hz range; thus, they were somewhat slower than waking alpha and were concentrated in the first half of the sleep period. The presence of an increased amount of SWS and the separate quantification of alpha-delta sleep resulted in a reduced amount of stage 2 sleep. Even if we added the time spent in alpha-delta sleep to that spent in stage 2 sleep, stage 2 sleep still remained 10% below normal values.

In patient 1, some light snoring occurred during various parts of the nights, but no relation was established between snoring and the presence of alpha-delta sleep or any other sleep stage. Alpha-delta sleep was accompanied by a reduced amount of spindles in patient 1: the total number of spindles per night varied between 7 and 13. The total number of spindles per night in patient 2 was 412 and 634.

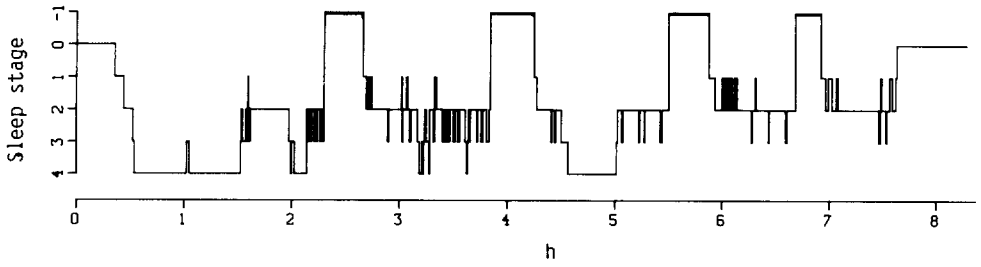

Fig. 2. Hypnogram of a sleep recording of patient 1. Y-axis: −1, stage REM; 0, awake; 1–4, stages 1–4

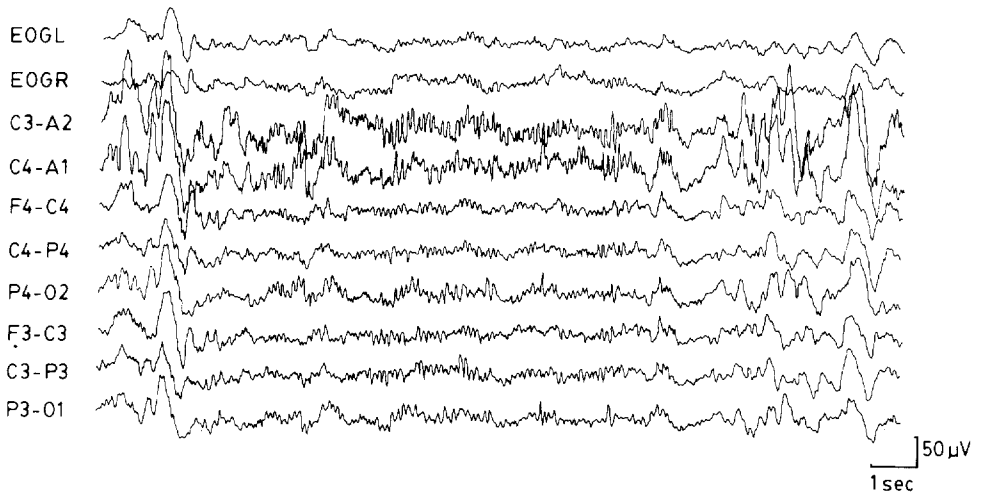

Fig. 3. Alpha-delta sleep as it occurred in frontal, central and occipital EEG leads

Discussion

In these patients with a selective central and peripheral noradrenaline deficit as a result of congenital DBH deficiency, a number of sleep characteristics were remarkable:

1. No subjective sleep complaints were reported; sleep was continuous and almost never interrupted by intermittent awakenings, except when the patients awakened to void urine due to "pressure-natriuresis".

2. The percentage of REM sleep was somewhat lower than normal. However, this abnormality was quantitatively certainly not large enough to imply an abnormal REM sleep pattern in these patients. In addition, a normal ultradian cyclicity in REM periods was observed.

3. In relation to a reduced amount of stage 2 sleep, a large amount of SWS was observed in both patients, in spite of the fact that naps occurred during day-time. In healthy subjects, naps have been shown to have a negative influence on the occurrence of SWS during the following sleep period [8].

4. The presence of alpha-delta sleep was more explicit in patient 1 than in patient 2.

Alpha-delta sleep in our patients partly consisted of the intrusion of the EEG alpha frequency into NREM sleep, as has been reported in psychiatric disorders [6], fibromyositis [15], and disorders of excessive somnolence [4]. However, the major part of the alpha-delta sleep pattern that we observed consisted of alternating patterns of regular alpha sleep with delta bursts, somewhat similar to the "micro-arousals" described by Lavie et al. [9], although this pattern did not present itself as short-lasting arousals but as continuous periods which could last for several minutes. The alpha-delta sleep pattern has been associated with complaints of non-restorative sleep [15] and suggests the presence of an arousal-related disorder, such as nocturnal myoclonus or sleep apnoea syndrome. We observed no clinical indication for the presence of either in our patients. The reduced amount of spindles in patient 1 corresponds with the findings of Hauri and Hawkins [6] where it concerns the lack of spindles during alpha-delta sleep. The number of spindles per night in patient 2 was not different from the data of healthy subjects reported by Silverstein and Levy [21].

Noradrenaline and REM sleep

Data with regard to the role of mono-aminergic neurotransmitters in sleep-wake regulatory mechanisms in man are usually based on the responses to agonist and antagonist drugs. Wakefulness and REM sleep are frequently coupled with increased and decreased noradrenergic activity, respectively [5]. A positive relation has been described with wakefulness, but the specific noradrenergic role in the initiation or production of REM sleep is more complex. Electrophysiological studies indicated that noradrenergic activity is involved in the slowing and cessation of REM-off cell discharge (in the locus ceruleus) before and during REM sleep, thereby emphasizing the inhibitory role of noradrenaline in the production of REM sleep [7, 18]. Gaillard [5] suggested that some noradrenergic neurons in the brain stem (locus ceruleus) are active when the subject is

awake and silent during REM sleep, and this by itself forms a prerequisite for REM sleep to appear. At the same time, the activity of other noradrenergic neurons (in midbrain, pons or subceruleus area) is necessary for the occurrence of REM sleep.

Our data indicate that noradrenaline is not essential for wakefulness during day-time, nor for the initiation, cyclicity and maintenance of (REM) sleep phenomena, although some alterations in duration of SWS, stage 2 and REM sleep do occur. These data favour the hypothesis of a noradrenergic modulatory role in (REM) sleep-generating mechanisms.

Dopamine and sleep

With regard to the central role of dopamine, it is believed that this neurotransmitter is primarily involved in behavioural arousal. In mammals, dose-related biphasic effects to dopamine agonist and antagonist drugs during sleep have been described [22]. In man, apomorphine caused a strong suppressant effect on SWS and REM sleep and increased stage 2 sleep [2]. In addition, it had sedative and sleep-inducing properties in normal and schizophrenic subjects [3]. Other studies with dopamine antagonists suggest a minimal role for dopamine in sleep [17].

The data of our patients contradict the SWS findings, but are to some extent in agreement with the REM sleep findings, since our patients showed a (slightly) reduced amount of REM sleep. It is possible that the excess of dopamine is active on dopaminergic receptors on noradrenergic neurons in the brain or that it exerts an action on alpha- and beta-adrenergic receptors, especially in the light of the denervation supersensitivity which can be demonstrated in these patients [12]. Since administration of alpha- and beta-adrenoceptor antagonists had no haemodynamic effects in our patients [11, 13], it is extremely unlikely that the increased concentrations of dopamine exerted actions on (central) adrenergic receptors. This hypothesis can be further tested by studying the effects of a dopamine antagonist and/or noradrenaline replacement therapy [12] on the sleep patterns of our patients.

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