Eur Arch Psychiatry Clin Neurosci (1994) 244:216–222

ORIGINAL PAPER

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CSF levels of diazepam-binding inhibitor correlate with REM latency in schizophrenia, a pilot study

Received: 23 March 1993 / Accepted: 9 June 1994

Abstract CSF diazepam-binding inhibitor-like immunoreactivity (DBI-LI) and polysomnography were studied in 28 drug-free male schizophrenic (DSM-III-R) patients. They underwent a three-night polysomnography evaluation and a lumbar puncture. CSF DBI-LI correlated positively with REM latency, the REM latency/2[d] nonREM period ratio and stage-4% sleep, and negatively with stage-1% sleep. CSF DBI-LI did not correlate significantly with duration of sleep or sleep latency. CSF DBI-LI during haloperidol treatment did not correlate significantly with sleep EEG measures. The results of this first study of the relationship between endogenous DBI and sleep in humans suggest that physiological effects of DBI other than interactions with the BZD/$GABA_A$ receptor complex may explain its positive effects on sleep. However, the absence of similar sleep data in normal subjects precludes us from establishing a specific relationship between DBI and sleep in schizophrenia.

Key words Diazepam binding inhibitor (DBI) Polysomnography · Schizophrenia

Introduction

Recently, diazepam-binding inhibitor (DBI), a 9-kD polypeptide, has been discovered in the brain as one of several endogenous ligands for BZD recognition sites (Guidotti et al. 1983; Ferrero et al. 1986). DBI is present in some GABA and other neurons (Alho et al. 1985), as well as in glial cells in the frontal cortex, hypothalamus, temporal lobe, and brain stem (Ferrero et al. 1986; Ferrarese et al. 1989). DBI is a precursor of a family of endacoids, some of which, like octodecaneuropeptide (ODN), for example, may act as negative, β-carboline-like, allosteric modulators of $GABA_A$ transmission (Costa and Guidotti 1987; 1991; Skolnick and Paul 1982). Others, such as triakontatetraneuropeptide (TTN) (Slobodyansky et al. 1989), act preferentially at the mitochondrial membrane BZD receptor (MBR) and stimulate neurosteroid synthesis (Papadopoulos et al. 1989; Costa and Guidotti 1991). DBI has other effects as well (Mikkelsen et al. 1987; Chen et al. 1988).

Benzodiazepines (BZDs) have a profound effect on sleep by decreasing sleep latency and transient awakenings after sleep onset, and increasing sleep duration (Borbély et al. 1991; Mendelson, 1990). More interesting are changes such as increasing REM latency (Borbély et al. 1991; Gaillard 1990; Feinberg et al. 1979; Kaye et al. 1976), decreasing Rapid Eye Movement (REM) sleep in high doses, and suppression of deep slow-wave sleep (Mendelson, 1990; Gaillard 1990; Bixler et al. 1978). REM sleep is not suppressed by all sleep-inducing doses, however (Vogel 1984).

Benzodiazepines (BZDs) have also been used in schizophrenia as an adjunct to antipsychotic drug treatment, in particular for the treatment of negative symptoms (Nestoros et al. 1982; Yassa et al. 1989; Couyon et al. 1989) or as potential antipsychotic agents (Wolkowitz et al. 1988; Jimerson et al. 1982; Lerner et al. 1979). Not all studies report positive results, however (Csernansky et al. 1988; Wolkowitz and Pickar; 1991). In addition, increased BZD receptor binding with (^{3}H)-flunitrazepam (Kiuchi et al. 1989) and γ-aminobutyric acid type A ($GABA_A$) receptor binding with (^{3}H)-muscimol (Toru et al. 1982; Hanada et al. 1987) have been reported in schizophrenic autopsy brains.

Sleep EEG studies have shown that schizophrenic patients have a variety of disrupted sleep parameters including an increased sleep latency, a shortened duration of sleep, a shortened first nonREM period or REM latency (Kupfer and Ehlers 1989; Jus et al. 1973; Zarcone et al.

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1987; Keshavan et al. 1990) and decreased slow-wave sleep (Feinberg et al. 1965; Caldwell and Domino 1967; Traub 1972; Reich et al. 1975; Hiatt et al. 1985). Most studies show that schizophrenic patients have more arousals and more superficial sleep, while others fail to find shortened REM latency or decreased slow-wave sleep (Keshavan et al. 1990; Kempenaers et al. 1988). Prior to the height of the psychotic decompensation, patients may actually stop sleeping (van Kammen and Kelley 1991), causing sleep results in schizophrenia to vary markedly.

We hypothesized that DBI-LI would be correlated with sleep EEG measures, based on the negative relationships of negative symptoms with CSF DBI (van Kammen et al. submitted), with REM latency (Tandon et al. 1989) and slow-wave sleep (van Kammen et al. 1988), the potential therapeutic effects of BZDs, and the reported decreased total sleep, slow-wave sleep and REM latency in schizophrenic patients.

Methods

Subjects

After signing an informed consent form for their procedures, 28 physically healthy, male psychiatric patients with a diagnosis of schizophrenia (DSM-III-R) (American Psychiatric Association 1987) participated in a combined CSF and polysomnography study following admission to the Schizophrenia Research Unit (SRU) at the Department of Veterans Affairs, Medical Center, Highland Drive, in Pittsburgh, PA. All subjects were screened with a complete physical, neurologic, and psychiatric evaluation conducted by a board-certified psychiatrist. Trained staff obtained the diagnostic data from a structured interview using the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) (Spitzer and Endicott, 1979), and a DSM-III-R checklist. Patients who met DSM-III-R criteria for alcohol or substance abuse and/or dependence or other axis-I diagnoses were excluded from the study. All clinical information was evaluated in a multidisciplinary diagnostic conference. All subjects were put on a low-monoamine and caffeine-free diet upon admission. Subjects were not allowed to nap during the day, as this would affect sleep parameters at night.

The 28 drug-free patients participating in the present study were from the 67-patient sample in whom we described the relationship between CSF DBI and schizophrenia (van Kammen et al. 1993). They had a mean age of 33.9 ± 6.4 years (24–45). They had been ill for 10.2 ± 6.5 years (0.5–23) with a mean age of onset of 23.7 ± 3.8 years (17–31). They had been without any other medication or drugs for at least 12 days prior to the sleep studies (mean ± SD: 38.4 ± 12.5 days; range 12–57 days) and 15 days before the lumbar puncture (LP), except for one severely relapsed patient who was drug-free for 8 days. Of the 28 drug free patients, 17 were tested before haloperidol treatment was discontinued. Three patients had never received antipsychotic medications. The age, duration of illness, and age at onset of illness were for the haloperidol treated patients 35.3 ± 6.3 years, 10.9 ± 6.8 years, and 24.5 ± 4.0 years, respectively. They were treated with an average dose of 9.1 ± 6.9 mg/day haloperidol (range 2–30 mg/day), that was associated with haloperidol levels of 14.2 ± 17.8 ng/ml (range 0.9–76.4 ng/ml).

Patients were rated daily by the nursing staff on the global psychosis, depression, anxiety, and mania items of the Bunney-Hamburg scale (Bunney and Hamburg 1963). The therapists rated patients weekly on the Brief Psychiatric Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982). Weekly meetings were conducted to ensure interrater reliability at greater than 85% for all behavioral measures. Patients were either clinically stable (no change in behavior compared to during haloperidol treatment) or relapsed (an increase of an average of 3 points in daily B-H psychosis ratings over 3 days) (van Kammen et al. 1989).

Polysomnography

As previously described (Neylan et al. 1992), 3 nights of polysomnography were performed during the patient's regular sleeping hours. Prior to the sleep studies, the patients were rated for sleep duration and disturbances by visual checks every 30 min. Those patients with sleep problems, including snoring, observed by the night nursing staff prior to testing were screened with the full clinical polysomnography montage; patients with sleep apnea were excluded from the sample. Sleep was recorded on a 20-channel polygraph (Grass-System 81). The parameters recorded included an electroencephalogram (EEG), electro-oculogram (EOG), and a submental electromyogram (EMG), in accordance with standardized guidelines (Rechtschaffen and Kales, 1968; Thase et al. 1986; Neylan et al. 1992). The ratio of the first nonREM period over the second nonREM period was used as an indication of REM pressure (Kupfer et al. 1990).

Lumbar puncture

Lumbar punctures (LPs) were performed in the morning after the third sleep study night in 21 patients. In 5 other patients, the LP was performed either the morning before or within 4 days after the sleep study. Spinal fluid was obtained according to established procedures (van Kammen and Sternberg 1980) with patients in the lateral decubitus position between 7:30 and 8:30 a.m. after bed rest and having fasted since 10:30 pm the previous night. CSF was collected on ice in 12-ml pools, that were divided into 0.5 and 1.0 ml aliquots. These samples were stored at –80° C until assay.

Radioimmunoassay of DBI-LI

CSF samples were assayed for DBI-LI as previously described (Guidotti et al. 1983; Barbaccia et al. 1986). The standard curve for human DBI was linear between 0.5 and 5.0 ng of human DBI per tube, and blank values (no antiserum) were constantly below 5% of the maximal human DBI ^{125}I bound (30–40% of the total). Standard DBI or CSF samples run in triplicate or duplicate had an intraassay variability of less than 5%. The interassay variability was less than 10% (Barbaccia et al. 1986). Barbaccia et al. (1986) observed that human DBI-LI from CSF of normal or depressed subjects had retention times identical to that of authentic DBI on reverse phase high-pressure liquid chromatography. CSF DBI-LI was not affected by prolonged freezer storage at –80° C (van Kammen et al. 1993).

Statistics

Values are expressed as means ± standard deviation (SD) of the mean. The individual sleep parameters from the second and the third nights of polysomnography were averaged for statistical analyses. In one relapsed patient, only two nights of sleep EEG were available. Sleep of relapsers and nonrelapsers were compared with two-tailed *t*-tests. Two-tailed Pearson product moment correlation coefficients were used to test the relationships between CSF DBI-LI and sleep EEG measures.

Table 1 Means and standard deviations of the polysomnographic measures in the total group ($n = 28$)

Sleep continuity	
Total recording period (min)	426.0 (26.8)
Sleep latency (min)	79.1 (77.1)
Awake time (min)	36.8 (36.7)
Time spent asleep (min)	302.3 (85.5)
% Awake time	0.14 (0.17)
Sleep efficiency	70.9 (20.1)
Sleep maintenance	89.7 (10.3)
Sleep architecture	
Stage 1 %	6.5 (4.5)
Stage 2 %	60.8 (12.1)
Stage 3 %	7.2 (5.8)
Stage 4 %	1.4 (2.5)
Delta sleep %	8.5 (7.1)
Ratio 1st NREM/2nd NREM period	0.86 (0.50)
REM measures	
REM time (min)	70.6 (27.8)
REM latency (min)	66.9 (32.2)
Rem latency – awake time (min)	64.1 (29.1)
REM activity	79.0 (40.4)
REM density	1.1 (0.3)
REM %	21.7 (7.3)
# of REM periods	2.9 (0.98)

Results

Table 1 shows the mean values of sleep continuity, sleep architecture and REM measures of the 28 drug-free patients. In Table 2 the relationship of CSF DBI-LI and polysomnographic measures in the drug free patients are displayed. CSF DBI-LI levels for the total group were 0.90 ± 0.21 pmol/ml, which was not significantly different from the those of the larger study or the normal controls (van Kammen et al. submitted). CSF DBI-LI correlated significantly with the first nonREM period (REM latency) ($r = 0.42$, $P = 0.029$) (Fig. 1), the first nonREM period minus awake time ($r = 0.46$, $P = 0.017$), the ratio of first to second nonREM period ($r = 0.57$, $P = 0.006$) (Fig. 2), stage 1% ($r = 0.43$, $P = 0.024$), and stage 4% ($r = 0.38$, $P = 0.045$), but not with sleep latency, duration of sleep, or other stages of sleep. All the significant relationships remained significant when age was used as a control variable (data not shown).

Relapsers slept significantly less (261 ± 88.5 vs 333 ± 71.1 min, $P = 0.025$), less efficiently (60.2 ± 19.7 vs $79.0 \pm 16.8\%$, $P = 0.011$), and had less stage 2 sleep (158.8 ± 58.6 vs 203.3 ± 44.2 min, $P = 0.03$). CSF DBI-LI levels were not significantly different between relapsers and stable patients (0.83 ± 0.16 vs 0.95 ± 0.24 pmol/ml, P = NS). Conceivably, some of these drug-free stable patients could have gone on to relapse in the subsequent weeks if they had remained drug-free.

None of the relationships of the sleep measures and CSF DBI-LI during haloperidol treatment reached significance (data not shown). The dose of haloperidol ($r = -0.46$, $P = 0.06$) and the haloperidol levels ($r = -0.31$, P = NS) correlated nonsignificantly with CSF DBI-LI.

Table 2 REM latency, REM density, the ratio of the first over the second nonREM period, stage-1 sleep % and stage-4 sleep % were significantly correlated with CSF DBI-LI in the entire group. In the clinically stable patients similar but nonsignificant correlations were observed, but with less varied values than in the relapsers. (data not shown)

Sleep continuity	
Total recording period (min)	$r = -0.09$ P = NS
Sleep latency (min)	$r = 0.02$ P = NS
Awake time (min)	$r = -0.28$ P = NS
Time spent asleep (min)	$r = 0.07$ P = NS
% Awake time	$r = -0.29$ P = NS
Sleep efficiency	$r = 0.09$ P = NS
Sleep maintenance	$r = 0.29$ P = NS
Sleep architecture	
Stage 1 %	$r = -0.43$ $P = 0.024$
Stage 2 %	$r = 0.11$ P = NS
Stage 3 %	$r = -0.09$ P = NS
Stage 4 %	$r = 0.38$ $P = 0.045$
Delta sleep %	$r = 0.06$ P = NS
Ratio NREM1/NREM2 period	$r = 0.57$ $P = 0.006$
REM latency (min)	$r = 0.42$ $P = 0.029$
Rem latency – awake time (min)	$r = 0.46$ $P = 0.017$
REM measures	
REM time (min)	$r = 0.06$ P = NS
REM activity	$r = -0.13$ P = NS
REM density	$r = -0.34$ $P = 0.083$
REM %	$r = -0.04$ P = NS
# of REM periods	$r = -0.05$ P = NS

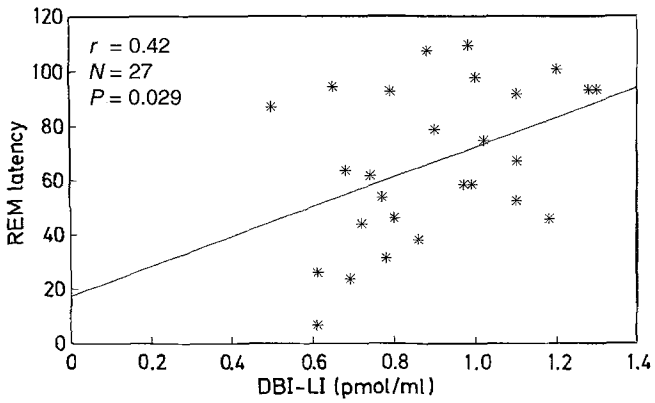

Fig. 1 Relationship between the furation of first nonREM period and CSF DBI-LI in male schizophrenic patients. $N = 27$ due to the fact that one subject did not fall asleep

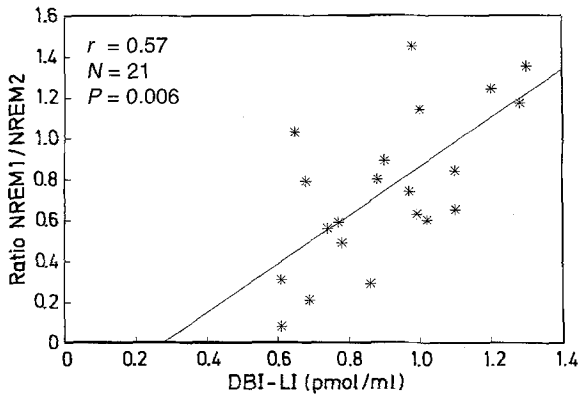

Fig. 2 Relationship between the ratio of the 1st nonREM period (REM latency)/the 2nd nonREM period and CSF DBI-LI

Log conversion of haloperidol measures lead to correlations of $r = -0.50$ ($P = 0.04$) and $r = -0.36$ ($P =$ NS), respectively.

Discussion

Our data indicate that in drug-free but not in haloperidol treated patients CSF DBI-LI correlated significantly with the length of the first nonREM period or REM latency and percent stage 4 sleep. CSF DBI-LI was unrelated to sleep latency and duration, which are modified by the administration of hypnotic BZDs (Mendelson and Martin 1990). These positive relationships of CSF DBI-LI with REM latency are similar to what has been observed with BZDs, while the relationship with stage 4 sleep is consistent with an effect opposite to BZDs (Borbély et al. 1991; Feinberg et al. 1979). However, the total amount of stage 4% was very low in our patients, particularly in the relapsers, whereas no significant differences in CSF DBI-LI between those with and without stage 4 sleep were observed. This suggests that other factors maintaining or suppressing slow-wave sleep may be involved, and that the relationship with stage 4% needs to be questioned as a possible chance finding. The positive relationship with the 1st/2nd non-REM period raises the possibility of suppression of the first REM period by DBI.

Lower CSF DBI-LI levels were associated with greater REM density, which is also different from what is observed with higher doses of hypnotic BZDs (Kaye et al. 1976); but BZDs may not change REM sleep in sleep-effecting doses (Vogel 1984).

Before discussing our findings further, we will address some methodological tissues. First of all, the CSF clearance rate and the origin of CSF DBI-LI are unknown. This peptide is the precursor of a family of peptides that may all have modulatory effects on sleep and behavior. Secondly, there may be a diurnal rhythm in DBI that affects sleep which is not reflected in the morning measure in the CSF. If there is a diurnal rhythm in DBI levels, however, the morning measure may be the basal level or may relate to the trough or peak. The significant relationships of CSF DBI with sleep EEG and behavior confirm that CSF DBI-LI reflects brain DBI levels. In addition, CSF obtained in the morning may relate to CSF DBI-LI levels 8 hours previously, because CSF is replaced over an 8-hour period, while CSF DBI-LI does not change that much from morning to morning. On the other hand, although there is no evidence that BZDs affect circadian rhythms in humans, the DBI rhythm may be different in schizophrenic from normal control subjects. Thirdly, we did not find significant relationships with SWS but a positive one with 4% sleep. The staging of sleep EEG was not designed to evaluate biological parameters or drug effects. Computerized spectral analysis may provide a better measure for the sleep measures related to DBI, because decreases in amplitude of SWS, as with hypnotic BZDs, may appear as decreases in SWS when visually scored (Feinberg et al. 1979).

When we looked at the relationships between CSF DBI-LI and the sleep evaluation the night immediately before the LP in the total group (N = 19), none of the relationships was significant, although in the same direction, which suggests that night to night variations in sleep EEG may be greater than the changes in CSF DBI-LI, or, not surprisingly, that sleep EEG measures from night to night are influenced by other mechanisms as well, unrelated to DBI. Only by removing some of the night-to-night variations by averaging the values did we observe the relationships. Inclusion of the relapsed patients, in whom the relationships were weaker than in the more clinically stable patients, strengthened the significance, suggesting that the relationships with CSF DBI-LI are under mixed trait/state influences.

Several groups (Mendelson and Martin 1990; Gaillard and Blois 1990), exploring the role of the BZD/$GABA_A$ receptor complex in sleep in rats and humans, concluded that BZD binding but not $GABA_A$ binding affected sleep, including the first nonREM period. They concluded that hypnotic BZDs do not exert hypnotic effects through altering BZD/GABAergic mechanisms. Particularly, the BZD receptor involved in anxiety may not be involved. These observations suggest that some BZD-related sleep

effects may be mediated indirectly through the mitochondrial membrane BZD receptor rather than directly through the GABA receptor complex, which is consistent with our present interpretations. We suggest that the interaction of DBI or its posttranslational cleavage products, such as TTN, may interact with the MBR, leading to stimulation of neurosteroid synthesis (Costa and Guidotti 1991; Besman et al. 1989). Recent evidence that steroids interact with GABAergic function either positively or negatively (Weinenfeld et al. 1980; Roselli and Snipes, 1984; Majewska et al. 1986; 1990; Miller et al. 1988) may shed light on these findings. This raises the possibility that the brain's own steroids play a role in sleep as well as in schizophrenia (van Kammen et al. 1993). Whether these animal data have any relevance for our study remains to be seen, particularly because other physiological effects are attributed to DBI, such as binding to acyl-coenzyme A and termination of fatty acid synthesis (Mikkelsen et al. 1987), and inhibition of glucose-induced insulin release from pancreatic islets (Chen et al. 1988). Insulin in the brain affects slow-wave sleep, as well. On the other hand, Mendelson (1990) showed that sleep-inducing BZDs had an arousing effect when microinjected into the dorsal raphe in very low doses.

The relationships between CSF DBI-LI and sleep measures are consistent with the negative relationships observed with anxiety, paranoia, and negative schizophrenic symptoms. They are not similar to the classic anxiogenic effects of BCs, and therefore may not be directly mediated through negative allosteric modulation of the $GABA_A$ receptor complex. Other biochemical factors may affect REM latency, e.g., delta sleep-inducing peptide (Obal 1986; van Kammen et al. 1992b), chromogranin A (van Kammen et al. 1992a), interleukins and other peptides (Opp et al. 1991; Krueger 1985). Our findings of positive relationships between CSF DBI-LI and sleep measures suggest that DBI in the physiological range may regulate stage 4 sleep or that mechanisms involved in slow-wave sleep also affect DBI. This all may be a part of the normal stress management of sleep. Because lower CSF DBI-LI was associated with more superficial sleep, DBI may also affect daytime arousal and attention. These relationships between endogenous DBI and sleep EEG reported for the first time in humans invite further study, particularly with a normal control group, to determine the relevance and the specificity of these findings for schizophrenia.

Acknowledgements The authors thank the patients and nursing staff of the Schizophrenia Research Unit under the leadership of Doris McAdam RN for their participation and collaboration. Deborah Lucas RN and Linda Augustine provided technical assistance with the sleep studies. Partial funding for this project was provided to Dr. van Kammen by the Highland Drive VAMC, the Department of Veterans Affairs Research and Development Service (Merit Review), The American Defenders of Bataan and Corregidor Medical Fund, and the National Institute of Mental Health (RO1MH44-841).

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