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ORIGINAL PAPER

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Polysomnographic comparison between patients with primary alcohol dependency during subacute withdrawal and patients with a major depression

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Abstract Complex neurobiological models based on animal research have been formulated in an attempt to explain the cyclic pattern of nonREM and REM sleep. The "reciprocal interaction model" of nonREM and REM sleep regulation, which has been updated to incorporate new evidence is still the most convincing. Therefore it is reasonable to apply this model also to REM sleep abnormalities such as shortened REM latency and increased REM density, observed in patients with depression and alcohol dependency.

In a retrospective analysis baseline data from 40 subjects with primary alcohol dependency are compared with a group of 40 patients diagnosed with major depression (diagnoses according to DSM-III-R) and healthy subjects. All alcohol dependent patients were examined in the sleep laboratory during subacute withdrawal at least 7 days off medication and after at least 14 days of abstinence. The patients with major depression (at least 7 days off psychoactive medication) and the healthy subjects had been examined previously by polysomnography during the last few years in the context of various studies and were assembled from our database to match the group of alcohol dependent patients with respect to age and sex.

Alcohol dependent patients exhibited similar disturbances in sleep continuity and REM sleep as depressed patients in comparison to healthy controls while parameters of sleep architecture were even more strongly disturbed in alcohol dependence.

While enhanced sensitivity of cholinergic receptors is the most likely explanation for the increase in "REM pressure" in depressives, this appears not to apply to alcoholics, who rather exhibit a decreased response to cholinergic stimulation. Thus, according to the reciprocal interaction model of nonREM- and REM sleep regulation and in contrast to the interpretation of the findings in depressed patients, an impaired aminergic rather than an increased cholinergic neurotransmission might be responsible for the increased REM sleep pressure in alcohol dependent patients. Alternatively or in addition the REM anomalies in alcoholic patients could also be due to adaptive regulatory processes during chronic alcohol consumption that lead to downregulation of $GABA_A$- and upregulation of NMDA-receptors or their intracellular signalling and become apparent with alcohol withdrawal. Such adaptive counterregulation might also explain the alterations in slow wave sleep found in alcoholics that are even more pronounced in these patients than in patients with major depression.

Key words polysomnography · REM sleep · alcohol dependence · major depression

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Introduction

Polysomnographic investigations in psychiatric patients, especially in depressives, have already a longstanding tradition. Work in depressed patients (for an overview see: Benca et al. 1992; Berger and Riemann 1993; Riemann et al. 2001) demonstrated that sleep in these patients is characterized by impaired sleep continuity (prolongation of sleep latency, increased frequency of nocturnal awakenings, early morning awakening) and a reduction of slow wave sleep (SWS). Changes of REM sleep distribution, i. e. shortened REM latency (= interval between sleep onset and the occurrence of REM sleep), prolonged duration of the 1st REM period, heightened frequency of rapid eye movements in REM sleep (= increased REM density), are prominent hallmarks of "depressed" sleep.

Complex neurobiological models based on animal research have been formulated to explain the cyclic pat-

tern of nonREM and REM sleep and the close association of REM sleep abnormalities with depressive psychopathology. The so-called reciprocal interaction-model of REM and nonREM sleep regulation at present is still the most convincing. Measurements of local neuronal activity in vivo and iontophoretic application of various neurotransmitter agonists and antagonists, have provided conclusive evidence that REM sleep is inhibited by the activation of aminergic neuronal activity (mainly in the dorsal raphé and the locus coeruleus) and stimulated by cholinergic neurotransmission of cell groups located in the gigantocellular field of the pontine tegmentum (Hobson et al. 1975, 1986; Hobson and Steriade 1986).

The central tenets of the reciprocal interaction-model are that noradrenergic neurons in the locus coeruleus (LC) and serotonergic neurons in the dorsal raphé nuclei (RN) inhibit REM sleep whereas cholinergic neurons in the laterodorsal tegmentum and pedunculo-pontine tegmentum (LDT/PPT) initiate and sustain REM sleep. Finally, these pontine cholinergic "REM-on" neurons excite via cholinergic projections the aminergic "REM-off" neurons in the LC and RN, while the latter feed-back via aminergic projections to inhibit activity of these cholinergic neurons (Hobson et al. 1975). The opposing sinus-like frequency of the activity of both neuronal groups corresponds to the regular 120-minute cycle of non-REM and REM sleep phases and is governed by these and other complex auto- and hetero-inhibitory and stimulatory connections within the so-called "REM-off" and "REM-on" neuronal networks. Novel in vitro and in vivo studies have corroborated this hypothesis and shown that the inhibitory effect of serotonergic neurotransmission on the pontine cholinergic neurons is indeed sufficient to suppress REM sleep (for review see: Sinton and McCarley 2000). In addition, several new findings have now been incorporated into this model, in particular the excitatory interaction between the pontine cholinergic neurons and glutamatergic neurons that contributes to a reinforcement of "REM-on" activity. A further modification was the consideration of the inhibitory effects of GABAergic neurons on both the aminergic neurons in the LC and RN and the mesopontine cholinergic neurons, which may either facilitate (via disinhibition of aminergic neurons) and inhibit (via inhibition of cholinergic neurons) REM sleep (for review see Pace-Schott and Hobson 2002).

It is reasonable to apply the reciprocal interaction-model to the explanation of REM sleep abnormalities observed in depression. McCarley (1982) hypothesized that the disinhibition of REM sleep in depression is due to an imbalance between aminergic and cholinergic neuronal systems and assumed that this imbalance consists of a preponderance of cholinergic over aminergic neuronal activity.

The stimulation of REM sleep by the application of cholinomimetics was introduced by Sitaram and Gillin (Sitaram et al. 1984) as the "cholinergic REM sleep induction test" (CRIT). Our group (Berger et al. 1989; Riemann und Berger 1989; Gann et al. 1992; Riemann et al. 1994 a, b) has shown that the well-known REM sleep disinhibition in patients with a major depression (Reynolds and Kupfer 1987; Gillin et al. 1984) is accentuated by application of cholinomimetics in the CRIT. These results provided further evidence for the explanatory value of the reciprocal interaction-model of REM sleep and nonREM sleep regulation and the cholinergic-aminergic imbalance model of affective disorder (Janowsky et al. 1972).

Based on further polysomnographic examinations of patients with personality, eating, obsessive, and anxiety disorders as well as with schizophrenic disorders (Berger et al. 1989; Hohagen et al. 1994; Lauer et al. 1990; Gann et al. 1992; Riemann et al. 1994a), we were able to show that disinhibition of REM sleep by the CRIT (including shortened REM sleep latency and increased density of the first REM period) is a typical feature of major depression. On the other hand we showed that depressive symptoms secondary to other psychopathological conditions are not linked to an increased sensitivity of the REM sleep system to cholinomimetics.

Our polysomnographic examinations of patients with primary alcohol dependency (Gann et al. 1997, 1998, 1999, 2001) aimed at clarifying the pathophysiological background of alcohol dependency with regard to cholinergic and aminergic neurotransmission as well as the potential predictive value of REM sleep abnormalities for relapses. Under baseline conditions (without cholinergic stimulation) the patients not only showed significant disturbances in sleep continuity and disturbances in sleep architecture, but also a significant increase of REM sleep pressure (higher density of the first REM phase, higher overall REM density and shortened REM latency). However, unexpectedly the REM sleep-inducing effect of cholinergic stimulation with galanthaminum hydrobromicum (CRIT) was less pronounced in the patients than in the control subjects. This result contrasts with the well-established finding in depressives, where the REM sleep-inducing effect of cholinergic stimulation with RS 86 is consistently more pronounced than in controls (Berger et al. 1989). The significantly increased "REM pressure" in alcohol dependent patients turned out as a positive predictor for alcoholic relapses at the 6-month follow-up.

In the present paper, for the first time, we have directly compared primary alcohol dependent patients (without clinically relevant depressive symptoms) with primary depressed patients to evaluate differences and similarities between both groups with respect to standard polysomnographic parameters. Based on the existing literature, we hypothesized that sleep abnormalities, particularly concerning REM sleep, would be more pronounced in patients with depression compared directly to alcohol dependent subjects.

The following retrospective analysis compares baseline data from 40 subjects with primary alcohol dependency, a group of 40 patients diagnosed with a major depression after DSM-III-R, and healthy subjects. All

alcohol dependent patients were examined by our group (Gann et al. 2001) under baseline conditions (without cholinergic stimulation) during subacute withdrawal in the sleep laboratory. The patients with major depression as well as the healthy subjects were polysomnographically examined by our group during the last few years in the context of various studies and were assembled as a new, randomly sampled group each time.

Methods

Subjects

All patients and control subjects underwent a thorough medical and psychiatric investigation as well as a physical examination, i. e. routine clinical and hematological laboratory examinations, urine analysis, electrocardiogram, electroencephalogram and magnetic resonance imaging (only patients). All results had to be within normal limits.

Patients with primary alcohol dependence

Forty patients (age 44 ± 9 years; range 24–62 years; 11 females: 44 ± 9 years; 29 males: 43 ± 9 years) with primary alcohol dependence (for exact clinical and demographic characteristics see Gann et al., 2001) were studied. They were admitted for treatment of alcoholism to a specialized ward that offers a 21-day inpatient treatment program for alcohol withdrawal and motivational therapy. The patients were asked and consented to participate in a multidisciplinary longitudinal investigation. As part of this study, subjects were asked to spend three consecutive nights in the sleep laboratory during the third weeks of hospitalization.

All patients met DSM-III-R criteria for alcohol dependency (the diagnosis was based upon a structured clinical interview, SCID, German version (Wittchen et al. 1989)). Eligible patients were required to have no other psychiatric illness or significant medical problem before the onset of alcoholism. Thus, we excluded patients with psychotic features, clinically significant cognitive impairment, antisocial personality disorder, substance abuse other than alcohol and nicotine, as well as major medical problems. No patient suffered from major depression at the time of investigation. All patients were free of psychoactive medication for a minimum of seven days preceding the investigation and had refrained from drinking alcohol for at least 14 days.

Patients with major depression

The group of patients with the diagnosis of major depression (according to DSM-III-R) had been examined polysomnographically by our group in the context of various studies in recent years. The 40 patients were selected from our database and the group of depressive patients was matched by age and gender with the group of alcohol dependent patients. Since the majority of the alcohol dependent patients were male, the gender distribution of the selected depressive "controls" does not correspond to the gender distribution of the overall population of depressive patients, in which the majority are women. The severity of the symptoms of depression was recorded before the beginning of the study according to the 21-Hamilton scale of depression, and had to be ≥ 18 points. All patients were free of psychoactive substances for at least seven days preceding the first night in the sleep laboratory. Patients who fulfilled the criteria of a further primary axis diagnosis of DSM-III-R, acutely suicidal patients and patients with psychotic symptoms were not included. The depressed sample consisted of 28 male patients with an average age of 42.2 ± 11.9 yrs and 12 female patients with an average age of 47 ± 11.9 yrs. The total sample had an average age of 43.8 ± 11.9 yrs.

Healthy controls

The control group comprised 40 subjects matched to the group of patients by age and gender. The control group (42.7 ± 10.8 years old) consisted of 29 men (42.2 ± 11.5 years old) and 11 women (44.2 ± 9.2 years old). The control group consisted of the subjects examined by Gann et al. (2001) as well as a further ten patients selected from our database.

Design

Patients and control subjects slept in the sleep laboratory for three nights. In the first (adaptation) night they were screened for sleep apnea and periodic leg movements during sleep (PLMS). Subjects with an apnea-hypopnea index > 10/hour or relevant PLMS were excluded from further study. The analysis of this study was based on the night following the adaptation night (2nd night).

Sleep recording and scoring

Sleep was recorded and scored according to standard criteria (Rechtschaffen and Kales 1968). Polysomnography encompassed EEG (C3-A2, C4-A1), horizontal and vertical eye movements and submental EMG. Recording of musculus anterior tibialis and of respiration (oral/nasal air flow and thoracal/abdominal respiratory effort and oxygen saturation) were performed only during the first night (adaptation) in the sleep laboratory. All recordings were performed from 23.00 to 7.00.

All sleep recordings were scored by an experienced rater "blind" to experimental conditions of the recordings. Recordings were analyzed by epoch (30 s length). The following sleep parameters were determined: total sleep time (min), sleep efficiency (% = total sleep time/time in bed x 100), latency to stage 2 (sleep latency in min, i. e. time from lights out until the first occurrence of stage 2) and latency to stage REM (min) (i. e. time from the first occurrence of stage 2 until the first occurrence of REM sleep), number of wake periods; wake, stage 1, stage 2, stage 3, stage 4, SWS (stages 3 and 4 combined) and REM expressed as % SPT (= Sleep Period Time = time from sleep onset until final awakening).

The variable "REM pressure" was calculated by means of a factorial analysis (principal component analysis, PCA) based on the parameters REM density in REM sleep period 1, REM (% SPT) and REM latency, as suggested by Gillin et al. (1994).

Statistics

Arithmetic mean and SD were calculated within groups. For the analysis of the sleep parameters a two-factorial ANOVA was used with consideration given to gender, corrected according to Greenhouse and Geiser's method. The individual contrasts of the factor "group" were calculated using post hoc Scheffé tests. A logarithmic redistribution was applied to parameters with an abnormal distribution of individual values. The modus of these values lay either at the upper limit (sleep efficiency) or at the lower limit (awake during the time for falling asleep as well as for percentages of the stages awake, 1, 3 and 4 of the sleep period) of the range of values. The decade logarithm was applied each time. All calculations were made using the SPSS statistics program package. The level of significance was set at $p < 0.05$ for all tests. The individual levels of significance were represented as follows: $p < 0.05 = *$, $p < 0.01 = **$ and $p < 0.001 = ***$.

Results

In order to ascertain how much the polysomnographic sleep pattern of patients with primary alcohol dependency after two to three weeks of abstinence differs from patients with a major depression and from healthy con-

Table 1 Group averages and results of the ANOVA with factors GROUP and GENDER. The 3 rightmost columns show the group contrasts (post hoc Scheffé tests). Significant values ($p < 0.05$) are indicated in bold print

Sleep parameter	Alcohol dependent patients	Controls	Depressives	Group df = 2; 114		Gender df = 1; 114		Group x Gender df = 2; 114		p Alc-Contr	p Depr-Contr	p Alc-Depr
	Mean (σ)	Mean (σ)	Mean (σ)	F	p	F	p	F	p			
Sleep continuity												
Sleep onset latency	18.06±12.93	13.19±10.30	16.69±11.91	1.65	0.196	0.02	0.878	2.55	0.082	0.179	0.409	0.870
Number of awakenings	25.20±8.89	16.70±11.78	23.63±13.51	4.94	**0.009**	1.33	0.252	0.12	0.883	**0.006**	**0.032**	0.832
Total sleep time	403.13±41.54	427.00±32.51	377.15±51.64	8.96	**0.000**	0.59	0.446	1.74	0.181	**0.046**	**0.000**	**0.027**
Sleep efficiency	84.60±7.99	89.33±6.83	83.47±9.79	3.89	**0.023**	0.69	0.406	2.17	0.119	**0.040**	**0.008**	0.828
Sleep architecture												
Wake % SPT[1]	9.85±5.93	6.40±6.02	11.56±8.87	2.74	0.069	0.23	0.635	2.94	0.057	0.091	**0.005**	0.551
S[2]1 % SPT	11.28±4.15	7.45±4.46	7.72±3.93	8.30	**0.000**	11.10	**0.001**	0.04	0.960	**0.000**	0.957	**0.001**
S2 % SPT	54.19±5.95	57.59±7.36	53.71±9.61	2.17	0.119	0.01	0.907	1.40	0.250	0.153	0.088	0.963
S3 % SPT	0.88±2.63	4.79±5.03	4.79±6.28	7.29	**0.001**	4.20	**0.043**	0.34	0.710	**0.002**	1.000	**0.002**
S4 % SPT	0.18±1.03	0.62±2.07	0.63±1.63	0.83	0.437	0.43	0.512	0.56	0.570	0.490	1.000	0.480
SWS[3] % SPT	1.06±3.31	5.41±6.49	5.42±7.70	5.64	**0.005**	2.09	0.151	0.43	0.652	**0.008**	1.000	**0.008**
REM sleep												
REM[4] latency	51.69±27.10	72.98±33.63	58.06±38.77	3.04	0.052	5.32	**0.023**	0.35	0.705	**0.018**	0.136	0.691
REM % SPT	23.21±5.88	22.54±4.61	21.28±5.59	1.49	0.231	0.01	0.929	0.36	0.702	0.861	0.583	0.287
REM density	38.36±11.94	25.51±8.15	33.14±11.09	13.74	**0.000**	1.11	0.295	0.48	0.618	**0.000**	**0.007**	0.091
REM density 1st period	30.84±15.55	20.29±11.22	27.66±15.27	6.06	**0.003**	0.47	0.495	0.50	0.606	**0.005**	0.073	0.609
REM pressure	0.33±0.95	−0.26±0.79	−0.03±1.14	3.76	**0.026**	2.45	0.120	0.33	0.721	**0.027**	0.569	0.256

[1] sleep period time; [2] stage; [3] slow-wave sleep; [4] rapid eye movement sleep

trols, the corresponding polysomnographic characteristic sleep values of the three samples are compared. The three groups were matched as closely as possible by age and gender. In the illustrations, the sleep parameters whose single values are not normally distributed and have undergone logarithmic transformation are shown next to the transformed values.

A two-factorial ANOVA was carried out in order to ascertain the influence of the variable "gender" on the polysomnographic data.

Since due to the exact matching of the groups, significantly fewer women were included than men, the interpretation of gender effects has to be considered explorative.

No significant interaction was found between the factors group and gender.

Significant group effects were found for total sleep time, sleep efficiency, number of awakenings, stage 1 (%SPT), stage 3 (% SPT), SWS (%SPT), REM density and REM pressure. For REM latency, the group effect was almost significant ($p = 0.052$). Significant gender effects were observed for stage 1 (%SPT), stage 3 (% SPT), and REM latency.

Sleep continuity

The following findings were significant (see Fig. 1): The number of awakenings were higher and total sleep time was lower in both the alcohol dependent and the depressed patients as compared to the healthy subjects; the total sleep time of depressed patients was shorter than that of alcohol dependent patients. The sleep efficiency of alcohol dependent and depressed patients was lower than that of the healthy control group. In summary, both groups of patients showed a comparably disturbed sleep continuity.

Sleep architecture

The following findings were significant (see Fig. 2): The wake time (%SPT) was higher in both patient groups than in the healthy subjects. Stage 1 (%SPT) was increased in the alcohol dependent compared to the depressed patients and the control group. SWS (%SPT) was decreased in the alcohol dependents compared to the depressed patients and the control group. In summary, slow wave sleep was more clearly diminished in the alcohol dependent patients than in the depressed patients.

REM sleep

The following findings were significant (see Fig. 3): Alcohol dependent patients had a significantly shorter REM latency than the healthy control group. REM density was increased in the alcohol dependent and the depressed patients compared to the healthy control group. REM pressure was higher only in the alcohol dependent patients in comparison to the healthy control group. In summary, both groups of patients show REM sleep disinhibition – the alcohol dependent patients even more pronounced.

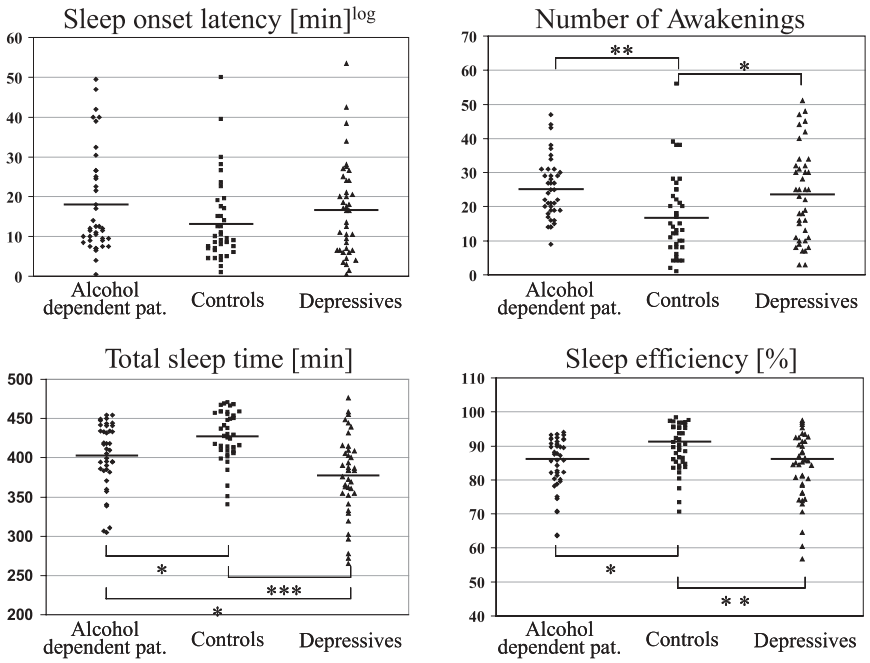

Fig. 1 Comparative sleep parameters for sleep continuity of alcohol dependent patients during subacute withdrawal, patients with major depression and healthy controls. Parameters marked [log] indicate a logarithmic transformation, whereas retransformed values are displayed

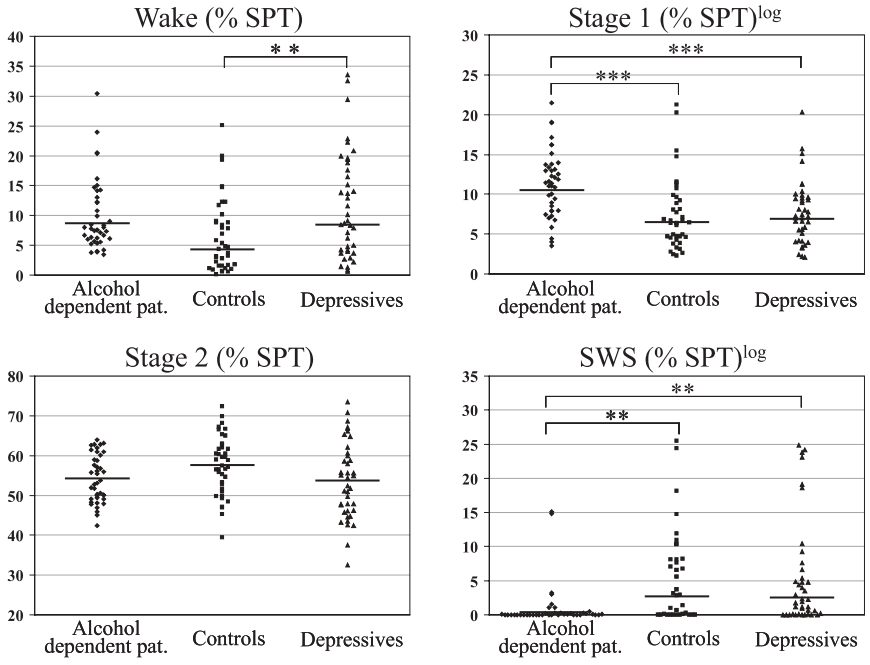

Fig. 2 Comparative sleep parameters for sleep architecture of alcohol dependent patients during subacute withdrawal, patients with major depression and healthy controls. Parameters marked [log] indicate a logarithmic transformation, whereas retransformed values are displayed

Gender differences

GENDER was included in the factorial ANOVA design because sleep may be altered differently in male and female patients. It should be noted that the gender comparison was not the primary aim of the current study; since our depressed sample was composed according to the observed gender ratio in alcoholics, females are largely underrepresented. Therefore the power of the statistical test for gender differences is lower than for group differences.

No significant GROUP x GENDER interactions were observed, i. e. no differences between alcohol dependent patients, depressives and controls that depended on gender.

In three variables, we observed group-independent effects of gender: S1 % SPT was reduced (by 3.15 ± 0.77 %), S3 % SPT increased (by 2.64 ± 0.87 %) and REM latency shortened (by 13.4 ± 6.4 minutes) in women relative to men.

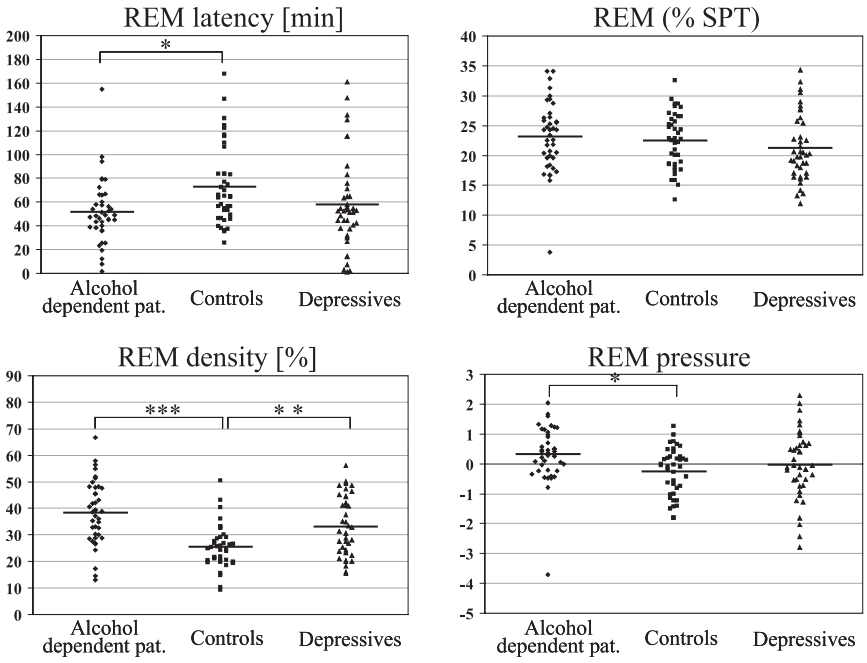

Fig. 3 Comparative sleep parameters for REM sleep of alcohol dependent patients during subacute withdrawal, patients with major depression and healthy controls

Discussion

The comparison of polysomnographic data of alcohol dependent patients, depressed patients and healthy controls shows that similar disturbances of sleep continuity and REM sleep regulation are present in alcohol dependent and depressed patients. However, in contrast to our hypothesis, sleep architecture is even more strongly impaired in alcohol dependent patients than in depressive patients. Thus, our hypothesis of less pronounced sleep abnormalities in alcohol dependence compared to depression was not confirmed. This unexpected finding is, however, not without precedence. Results of Moeller et al. (1993) and Clark et al. (1999) suggested earlier that disturbances in the sleep EEG of patients with alcohol dependence are at least as pronounced as those in the EEG of patients with primary major depression.

The data of alcohol dependent patients during subacute withdrawal presented here have been discussed by Gann et al. (1997, 1998, 1999, 2001) and are comparable to earlier findings (Gillin et al. 1986, 1990, 1994).

Polysomnographic data of the group with major depression are also in general accordance with the literature (Armitage und Hoffmann 2001; Riemann et al. 2001; Reynolds and Kupfer 1987).

According to the reciprocal interaction model the REM sleep disinhibition that is found both in alcoholics and in depressed patients under baseline conditions (without cholinergic stimulation) could, in principle, be explained in two ways. REM sleep disinhibition might either be due to decreased aminergic or to increased cholinergic neurotransmission. Earlier studies of depressed patients which applied the CRIT with the cholinergic agonist RS 86 have provided evidence for the latter alternative. They indicated a higher cholinergic receptor susceptibility of these patients towards cholinergic stimulation (Berger et al. 1989; Gann et al. 1992; Riemann et al. 1994b). However, as opposed to depressed patients, alcohol dependent patients do not exhibit a higher sensitivity to cholinergic stimulation (Gann et al. 2001).

It should however be borne in mind that two different forms of the CRIT were used in the two groups: While the patients with major depression were stimulated with RS 86 in the case of alcoholic patients galanthamine was used. While we cannot exclude that this difference in the procedure might affect the quantitative outcome of the CRIT, it is difficult to imagine how it might lead to an entirely different qualitative outcome in the two groups compared. The reduced response to cholinergic stimulation in alcoholics indicates that a subsensitivity of cholinergic receptors might be present in alcohol dependent patients. Janowsky et al. (1989) already reached this conclusion from their finding that an injection of physostigmin induced only minor alterations of the pulse rate and various behavioral parameters in intoxicated patients with primary alcohol dependency. Furthermore, Freund and Ballinger (1988) have demonstrated a reduced density of cholinergic and muscarinergic receptors in the frontal cortex of non-demented chronic alcoholics through brain autopsy. Thus, contrary to the findings in depressed patients, supersensitivity of cholinergic receptors cannot be responsible for the increase in REM pressure found in alcoholic patients. However the increased REM pressure in alcoholic patients might nevertheless be due to increased cholinergic neurotransmission but evoked rather by an enhanced activity of cholinergic neurons and thus increased release of acetylcholine. The subsensitivity observed in the CRIT could in this case be due to consecutive downregulation of cholinergic receptors,

which, however, would not fully compensate for the increased release of acetylcholine and thus still allow a rise in REM sleep parameters. If this were the case, galanthamine might not increase cholinergic transmission in alcoholics due to a ceiling effect. On the other hand, a severely impaired aminergic neurotransmission might also explain the increased REM sleep pressure in alcohol dependent patients under baseline conditions. This impairment might even overcompensate for a perhaps reduced cholinergic neurotransmission due to subsensitive receptors. Indeed, studies with patients and animal experiments have provided evidence that impaired serotonergic neurotransmission seems to be a potential marker of vulnerability for alcohol dependency (Roy et al. 1987; Sellers et al. 1992).

How chronic alcohol consumption might induce alterations in aminergic and/or cholinergic neurotransmission that contribute to the disturbances in the regulation of nonREM/REM sleep is unknown. However, more recent findings indicate that also GABAergic and glutamatergic neurotransmission plays a prominent role in the regulation of REM and nonREM sleep (for review see Pace-Schott and Hobson 2002). Both neurotransmitter systems are known to be important targets of the actions of alcohol in the brain.

Particularly well established are the effects of ethanol on GABAergic mechanisms (for review see Aguayo 2002). Acute alcohol intoxication often leads to reinforcement of neuronal inhibition mediated by $GABA_A$ receptors. There are, however, considerable differences in the sensitivity to such actions of ethanol that are apparently to some extent genetically determined (Harris and Allan 1989; Grobin et al. 1998; Poelchen et al. 2000) and due to differences in the pattern of $GABA_A$ receptor subunits or in the signal transduction mechanisms involved (Grobin et al. 1998; Proctor et al. 2003). On the other hand, chronic or chronically intermittent treatment with alcohol rather leads via biochemical adaptation to diminished GABAergic neuronal inhibition and to alterations of the subunit structure of the $GABA_A$ receptors (Cagetti et al. 2003; for review see: Grobin et al. 1998). The reinforcement by ethanol of GABAergic inhibition might explain why acute intake of alcohol intensifies nonREM sleep, since GABAergic neurons in the ventrolateral preoptic areal (VLPO) of the anterior hypothalamus are active during nonREM sleep and promote nonREM sleep by inhibition of the wake-active aminergic neurons in LC, RN and n. tuberomammilaris (TMN). The adaptive decrease of GABAergic inhibition after chronic alcohol treatment might, on the other hand, explain the increase of neuronal excitability and the decline of SWS during withdrawal.

Another well documented effect of ethanol is the inhibition of the NMDA subtype of glutamate receptors (for review see: Kumari and Ticku 2000; Wirkner et al. 1999). Like the effects of ethanol on $GABA_A$ receptors also its actions on NMDA receptors are quite variable, probably due to the heterogeneous subunit structure of these receptors. As in the case of $GABA_A$ receptors chronic treatment with ethanol also results in an adaptive regulation of NMDA receptors which counteracts the acute effects. Since NMDA receptors are inhibited by ethanol, their adaptation to chronic alcohol leads to upregulation of the number of receptors and consequently to an increased glutamatergic excitation associated with an enhanced disposition to seizures, a well-known symptom of alcohol withdrawal. The significance of glutamatergic neurotransmission in sleep regulation and of NMDA receptor mediated effects on sleep are insufficiently understood. Glutamate acts as the neurotransmitter of a population of neurons of the reticular activating system in the brain stem, which also control the cholinergic neurons in the basal forebrain (for review see Jones 2003). The inhibition of NMDA receptors induced by acute alcohol could thus contribute to the sedating, SWS promoting acute actions of alcohol, while the adaptive increase in sensitivity of NMDA receptors after chronic ethanol might be instrumental for the sleep disturbances and the REM disinhibition which are observed after chronic alcohol intake.

Alcohol might also influence the homeostatic regulation of sleep exerted by adenosine. At least two mechanisms appear to play a role in the effects of ethanol on adenosine (Overview: Dunwiddie 1999; Dunwiddie and Masino 2001): i) increase of the concentration of adenosine due to enhanced formation of AMP via metabolism of ethanol (Carmichael et al. 1991), ii) increase of extracellular adenosine by inhibition of adenosine transport (Diamond et al. 1991; Sapru et al. 1994). The ethanol induced increase in extracellular adenosine would reinforce the inhibitory action of adenosine on the cholinergic neurons in the LDT/PPT and basal forebrain and thus promote SWS. This effect could thus mediate at least in part the SWS-promoting action of acute alcohol intake. Chronic alcohol consumption induces also in this case (as in those of $GABA_A$ and NMDA receptors discussed above) an adaptive response which counteracts the acute action. In the case of adenosine, however, this counter regulation is mediated predominantly by adaptive changes in the sensitivity of signal transduction systems and thus pertains not only to adenosine receptors but also to other receptor systems (Sapru et al. 1994).

In summary our data show that alcoholic patients exhibit an even more pronounced increase in REM pressure than depressive patients as compared to controls but these abnormalities in alcoholics, unlike depressive patients, cannot be explained by an increased sensitivity to cholinergic stimulation. Thus, the pronounced abnormalities in sleep parameters in alcoholics might be due to enhanced activity of cholinergic neurons, impaired aminergic neurotransmission, or adaptive changes in NMDA receptors. In addition, adaptive changes in $GABA_A$ receptors and altered adenosine concentrations and/or signal transduction might be responsible for the particularly pronounced abnormalities in slow wave sleep observed in alcoholic patients. Further work will be needed to decide between these various potential mechanisms.

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