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COGNITIVE AND BEHAVIOURAL ASPECTS

Non-right-handedness and Free Serum Testosterone Levels in Detoxified Patients with Alcohol Dependence

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ABSTRACT — Aims: The influence of testosterone on the extent of hemispheric dominance has been discussed not just during the first two trimesters of pregnancy but also later in life. An increase in free serum testosterone levels has been found during and after the detoxification phase of patients with alcohol dependence. **Methods**: In 250 participants (125 men and 125 women) with alcohol dependence immediately after the direct withdrawal phase (Day 21) and in 250 healthy age- and gender-matched participants, free testosterone in the serum was determined and handedness was assessed as a peripheral marker of central hemispheric dominance. **Results**: Patients with alcohol dependence were 2.7-fold (odds ratio, OR: 2.66; 95% confidence interval, CI: 1.62–4.38) and men 4.1-fold (OR: 4.12; 95% CI: 2.44–6.98) more likely to be non-right-handed (NRH). In addition to male gender, non-right-handedness and alcohol dependence contributed statistically significantly to higher serum testosterone levels. Testosterone values of patients with alcohol dependence differed significantly between the four different Lesch subtypes; in particular, participants with alcohol dependence classified according to Lesch subtype IV were found to have significantly higher serum testosterone levels ($F = 20.5$; $P < 0.001$) when compared to participants classified according to Lesch subtypes I–III. **Conclusions**: An alteration of hemispheric dominance and thus an exogenously modifiable neuronal plasticity may be demonstrated directly on a population at risk.

INTRODUCTION

It is widely accepted that alcohol affects sexual hormone levels (Ruusa *et al.*, 1997). The general interaction between alcohol and testosterone has been the subject of several investigations (Ruusa *et al.*, 1997; Walter *et al.*, 2007). During detoxification, an increase in testosterone was described after 3 weeks of sobriety (Ruusa *et al.*, 1997). High alcohol consumption and tobacco use before detoxification may lead to higher testosterone levels before and after withdrawal (Walter *et al.*, 2007). This increase in free serum testosterone levels has been ascribed to acute alcohol consumption.

Hormones such as testosterone may influence hemispheric dominance as discussed in various endocrinological investigations (for review, see Habib *et al.*, 1995). They may influence hemispheric dominance through the life span in interaction with sexual hormones. Sex hormone levels are influenced by various conditions throughout life such as alcohol consumption, dependence and withdrawal (Sperling *et al.*, 2000).

According to the Geschwind–Bahan–Galaburda hypothesis (Geschwind and Galaburda, 1985), 'anomalous cerebral dominance' is usually defined via left-handedness and ambidexterity compared to subjects with standard left dominance (right-handers without familial sinistrality) (Tan, 1991; Tan and Tan, 2001). Mean serum testosterone levels were found to be significantly higher in adulthood with anomalous dominance when compared to those with standard dominance (Tan, 1991; Tan and Tan, 2001). This association might be due to a suppressing effect of testosterone on neuronal development of the left brain (Bryden and Bulman-Fleming, 1994; Bryden *et al.*, 1994), which may also be reflected in a reduced volume of the left hemisphere when compared to the right hemisphere in adulthood (Bryden and Bulman-Fleming, 1994; Bryden *et al.*, 1994). Anomalies in cerebral dominance, immune functioning, general personal abilities and neural crest development are hypothesized to interact due to high levels of prenatal testosterone. However, several reviews of the origins of the neural crest and its associations did not find empirical support for the testosterone hypothesis (Berenbaum and Denburg, 1995; Bryden and Bulman-Fleming, 1994; Bryden *et al.*, 1994).

The concept of hemispheric lateralization has led to controversies about the extent to which prenatal exposure to testosterone could have an influence on hemispheric dominance, not just in the developing brain (Berenbaum and Denburg, 1995; Dellatolas *et al.*, 1990; Habib *et al.*, 1995). According to more recent investigations, the influence of testosterone on the degree of hemispheric dominance should be discussed in the mature brain and not just in the prenatal phase (Cohen-Bendahan *et al.*, 2004; Tan, 1991; Tan and Tan, 2001). Higher serum testosterone levels were thus described in adults with anomalous hemispheric dominance and may have a life-long influence on cerebral lateralization (Tan, 1991). In particular, with regard to gender-specific aspects, a trophic effect of testosterone on the growth of the left hemisphere was even described in women (Tan, 1991).

The hypothesis of neuronal plasticity, which postulates the possibility of perpetually self-modifying neuronal networks, raised doubts about the purely intrauterine conditioning of the human brain (Povlishock *et al.*, 1992; Weinberger and McClure, 2002). Animal studies have revealed that individual differences in the expression of genes in brain regions that regulate stress reactivity could also be transmitted from one generation to the next by behaviour, not only through genomic mechanisms (Francis *et al.*, 1999). This dynamic principle of the plasticity and adaptivity of the brain continuing with ad-

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vancing age and its vulnerability to endogenous/exogenous noxae has been increasingly used to explain the complex interactions between sexual hormones, cerebral anatomy and function, and behaviour (Walsh and Opello, 1992).

A dynamic modifiability of clinical pictures was also implied in the study of addictive disorders using multidimensional classification systems (Cloninger *et al.*, 1988; Lesch and Walter, 1996). The system of Lesch (subtypes I–IV) includes genetic, developmental biological, socio-biographic and personality influencing factors (Biermann *et al.*, 2009). A computerized decision tree was developed, diagnosing the typology as follows (Lesch *et al.*, 1990; Lesch and Walter, 1996): subtype I (Model of Allergy) has an early and marked withdrawal syndrome, metalcoholic psychosis and alcohol withdrawal seizures; subtype II (Model of Anxiety and Conflict) is characterized by pre-morbid anxiety and conflict, lacking self-confidence and trying to solve these conflicts through excessive drinking behaviour; subtype III (Alcohol as Antidepressant) emerges mainly from a permissive alcoholic milieu with a predisposition for affective disorders and suicidality, and alcohol is applied as a means of self-medication; subtype IV (Alcohol as Adaptation) has pre-morbid cerebral damage with epilepsy and severe polyneuropathia and serious social problems predominantly since childhood, with cognitive deficits persisting long after alcohol withdrawal.

The aim of this study was to estimate serum testosterone levels during alcohol withdrawal and examine their relationship to cerebral dominance measured by means of handedness.

METHODS

Participants

This study was carried out in the Psychiatric University Hospital of Erlangen (Germany) and the Anton Proksch Institute of Vienna (Austria). The methodology has been previously described in detail elsewhere (Sperling *et al.*, 2000).

A total of 250 participants with alcohol dependence, 125 women and 125 men (age range: 19–69 years, mean age: 43.8 years; SD: 23.4 years), were admitted after the withdrawal phase (Day 21) to the study, and a gender- and age-matched group of healthy participants served as a control group.

Exclusion criteria (Sperling *et al*., 2000) were endocrinological tumours and the use of any steroid or medications with testosterone or testosterone interference within the last 8 weeks before the study parameters were tested. This information was retrieved from medical notes. The study was approved by the local ethics committee.

Experimental design

Handedness

Determination of handedness was carried out using the Shimizu design (Shimizu *et al.*, 1985). The Shimizu handedness questionnaire uses 13 daily activity items (such as writing with a pen, using a knife and using a pair of scissors) to define the degree of handedness (−1, left hander; 0, ambidextrous; +1, right hander). The sum score of all 13 single items defines the assignment of each patient to right-handedness, left-handedness and ambidexterity; the latter is included in the group of NRH.

Serum testosterone

In laboratory analyses, the total testosterone levels were measured in 3 mL serum, using electrochemiluminescence immunoassay technique, immediately after the withdrawal phase (on Day 21). For healthy adult men, the normal range for testosterone was 2.8–8.0 μg in male patients and 0.06–0.82 μg in female patients. All samples were collected at the same time, between 07:00 and 9:00 a.m. The chemical analyses of testosterone were conducted at the Laboratory for Clinical Neurochemistry at the University of Erlangen-Nuremberg.

Statistical methods

The odds of being NRH (left-handed) were calculated in a logistic regression model with NRH as the dependent variable and gender and group (participant with alcohol dependence or healthy participant) as independent variables. In a second step, the odds of being NRH were analysed in a stratum consisting of participants with alcohol dependence by computing gender-adjusted logistic regression models (using dichotomous dummy variables for the Lesch subtypes such as subtype II versus non-subtype II).

A general linear model with testosterone level as the dependent metric variable was computed. The dichotomous variables including gender, group and NRH were used as factor variables. Interaction models were also considered.

In a second step, testosterone levels in the stratum of participants with alcohol dependence were analysed using the same approach as before (instead of the factor group, dichotomous dummy variables for the Lesch subtypes were used).

All statistical tests were two-sided. The significance level was set at $\alpha = 0.05$. The statistical software package SPSS 16 for Windows (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

In a logistic regression model, participants with alcohol dependence were 2.7-fold (odds ratio, OR: 2.66; 95% confidence interval, CI: 1.62–4.38) and men 4.1-fold (OR: 4.12; 95% CI: 2.44–6.98) more likely to be NRH. Regarding the Lesch classification for patients with alcohol dependence, the odds (using gender-adjusted logistic regression models) of being NRH for a participant classified as Lesch subtype II were significantly lower compared to other Lesch subtypes (OR: 0.27; 95% CI: 0.13–0.56; $P = 0.001$). In contrast, the odds for a patient with alcohol dependence classified as Lesch subtype IV were significantly higher when compared to other Lesch subtypes (OR: 9.99; 95% CI: 4.75–21.02; $P < 0.001$). Based on the results of a general linear model, serum testosterone levels were dependent on sex ($F = 547.8$; $P < 0.001$), handedness ($F = 16.6$; $P < 0.001$) and alcohol dependence ($F = 34.8$; $P < 0.001$). All combination interactions were also significant. Thus, male sex, NRH and alcohol dependence contribute to higher serum testosterone levels (see Fig. 1).

This model was fitted with the classification variables for the four Lesch subtypes, resulting in four different models, and participants with alcohol dependence classified according to Lesch subtype IV were found to have significantly higher serum testosterone levels ($F = 20.5$; $P < 0.001$). Interactions

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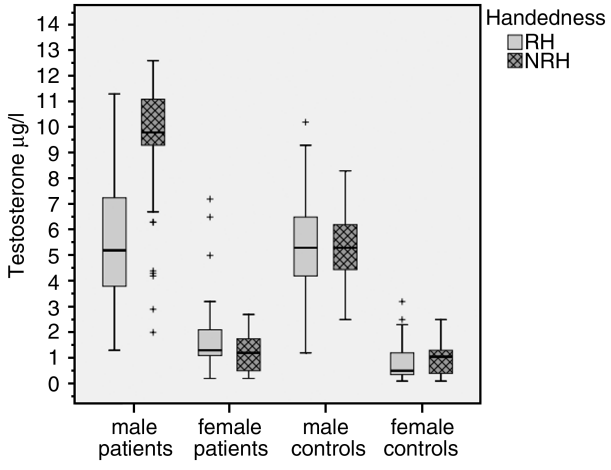

Fig. 1. Handedness and testosterone levels. Serum testosterone levels of 250 participants with alcohol dependence (125 men and 125 women) and 250 healthy participants without alcohol dependence (125 men and 125 women) with non-right-handedness (NRH) and right-handedness (RH). Plus symbols: cases with more than 1.5 box lengths from the upper or lower edge of the box. The box length is the interquartile range.

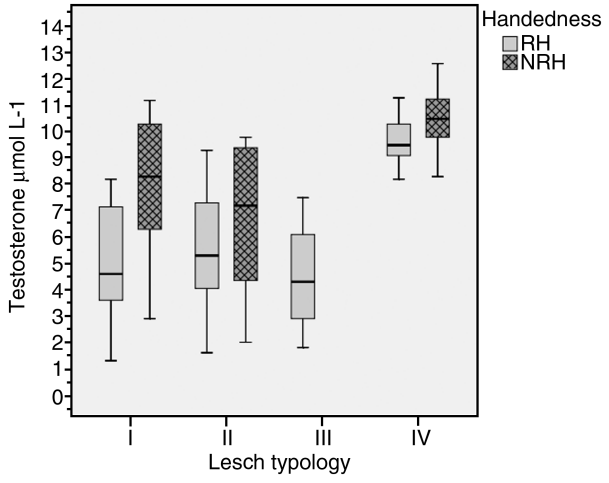

Fig. 2. Differences in Lesch's typology of male patients with alcohol dependence. Serum testosterone levels of 125 male alcohol-dependent patients with non-right-handedness (NRH) and right-handedness (RH).

between Lesch subtypes I and II, handedness and testosterone level could be found in a male stratum only, whereas NRH men with alcohol dependence had significantly higher testosterone levels than right-handed men (see Fig. 2).

DISCUSSION

Participants with alcohol dependence, particularly males, were more often NRH than controls. These findings are consistent with the results obtained by other studies on individuals with alcohol dependence describing a higher rate of non-right-handers than seen in the general population (London, 1987; London and Glick, 1988; McNamara *et al.*, 1994). However, the precise timing of determining handedness in those studies may not have been as closely defined (in our study: at Day 21 at the end of detoxification). Previous studies did not explore the association with serum testosterone concentration. The precise point in time during the detoxification phase is an important factor in determining the effect of elevated testosterone levels. Walter and colleagues (Walter *et al.*, 2007) found no increase in serum testosterone values during acute detoxification until 6 weeks after withdrawal when serum testosterone concentrations were positively correlated with the amount of the previous alcohol consumption.

In the present study, in participants with alcohol dependence classified according to Lesch subtype II, the proportion of NRH was significantly lower than in other Lesch subtypes, whereas the proportion of NRH in subtype IV was significantly higher. Serum testosterone levels in participants with alcohol dependence were observed to be higher than in healthy participants, particularly for male participants.

Previous work suggested that an increase in testosterone might be attributed to the withdrawal process (Ruusa and Bergman, 1996; Ruusa *et al.*, 1997; Walter *et al.*, 2007). An association was found between levels of testosterone and severity of withdrawal symptoms during alcohol detoxification in male alcohol-dependent patients. Participants with lower testosterone values tended to develop neurotic asthenic withdrawal syndromes, while participants with higher values were found to suffer from paranoid aggressive syndromes and often seizures (Ruusa and Bergman, 1996; Ruusa *et al.*, 1997).

A subtype-specific heterogeneity with regard to vulnerability factors has been described for the Lesch classification (Bleich *et al.*, 2004; Reulbach *et al.*, 2007a; Samochowiec *et al.*, 2008). The higher proportion of NRH within this subgroup has already been described elsewhere (Sperling *et al.*, 2000). As mentioned before, handedness may be modified by higher testosterone levels. This modification may be discussed in two models; in the context of the Geschwind–Bahan–Galaburda hypothesis, it could be hypothesized that higher testosterone levels may have a permanent effect on cerebral lateralization if it is initiated during the prenatal period. Subtype IV is characterized by pre-morbid cerebral damage and especially by cognitive deficits persisting after alcohol withdrawal. This subtype may be exceptionally vulnerable to testosterone effects such as prenatal induced left-hemispheric suppression. Vulnerability concepts in terms of handedness postulated in various psychiatric diseases (Reulbach *et al.*, 2007b; Zubin and Spring, 1977) usually refer to the first two trimesters of pregnancy (Beckmann and Jakob, 1994). Therefore, independently of the withdrawal process, higher testosterone values may be present in individuals with Lesch subtype IV prenatally, which would then offer a possible approach to explaining a higher NRH fraction of this subtype in the withdrawal-free phases. A decisive question in this connection, not yet addressed in our present design, would be the comparison of basal (withdrawal-independent) and withdrawal-specific testosterone values.

Therefore, independently of a permanent effect on cerebral lateralization, there may be a more dynamic influence of testosterone under changing conditions during lifetime (for example, induced by higher testosterone levels during withdrawal). The effect of a testosterone-induced left-hemispheric suppression (Tan, 1991), with a consecutive increase in the NRH fraction during lifetime, has been described by Tan. Individuals according to Lesch subtypes I and II are characterized by increased withdrawal craving and

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high comorbidity with anxiety and depression, and in this study, with statistically significant higher serum testosterone in participants with NRH compared to right-handed participants with alcohol dependence. In functional imaging investigations, the particular activation of right-hemispheric regions (e.g. amygdala, hippocampus) has been described in patients with strong craving (Schneider *et al.*, 2001). The strong association between NRH and testosterone in subtypes I and II may be explained here, perhaps in contrast to subtype IV, by a 'testosterone overflooding' effect. Again, a longitudinal design would be needed to gain a clearer insight into this complex interaction.

There is another limitation in the present study. Handedness patterns in families of participants were not tested in a standardized manner. Therefore, any questions regarding the genetic loading remained unanswered.

This investigation sheds some light on some unanswered questions.

(1) Does a change in hemispheric dominance occur at different clinical phases (e.g. acute withdrawal, long-term detoxification, free interval), depending on varying serum testosterone levels?

(2) Does the subtype-specific effect remain stable within the context of this course-orientated process?

The limitations and open questions should provide the basis for future longitudinal investigations, which may give a clearer understanding of exogenously modifiable neuronal plasticity in populations at risk.

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