NEUROBIOLOGY AND TREATMENT IN ALCOHOLISM—RECENT FINDINGS REGARDING LESCH’S TYPOLOGY OF ALCOHOL DEPENDENCE

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Abstract — Subtyping in alcohol dependence has become an important issue as studies have proposed different neurobiological mechanisms in alcoholism in the recent years. Studies have shown that alcohol dependence reflects a wide range of different phenotypes, including psychological, social, and neurobiological factors. Different ways of subtyping have been proposed in the last decades, one of them being Lesch’s typology of alcohol dependence. Recent investigations have shown that different subtypes of Lesch’s typology are associated with specific neurobiological factors which may have important implications for clinical practice. This applies in particular for genetic and neuroendocrinological factors, differences in the regulation of NMDA receptor-mediated glutamatergic neurotransmission, and in response toacamprosate and naltrexone treatment.

INTRODUCTION

Alcohol dependence is a highly relevant disease in clinical medicine. Social, psychological, and biological factors influencing the etiogenesis of alcohol dependence are manifold and subject to intensive research worldwide. Moreover, alcohol dependence is a disease particularly characterized by frequent but very different comorbidities. These comorbidities range from medical conditions associated with alcohol consumption such as liver cirrhosis or esophageal varices to psychiatric disorders such as depression, ADHS, personality disorders, or anxiety disorders. Many attempts to classify patients with alcohol dependence have been made in the past. These include biologically orientated typologies (Cloninger et al., 1988; Babor et al., 1992; Babor and Caetano, 2006) and classifications focusing on behavioral characteristics (Jellinek, 1960). The Lesch typology, which is widely used in Europe and especially in German-speaking countries, tries to integrate biological, social, and psychological factors in one classification (Lesch et al., 1990; Lesch and Walter, 1996). The typology differentiates four subtypes: type 1 (model of allergy) consists of patients with heavy alcohol withdrawal symptoms who tend to use alcohol to weaken detoxification symptoms. Patients of type 2 (model of anxiety or conflict) are characterized by using alcohol as self-medication because of anxiolytic effects. The main characteristic in type 3 patients is an underlying affective disorder (alcohol as an antidepressant) (Kiefer and Barocka, 1999). Type 4 patients (alcohol as adaptation) show pre-morbid cerebral defects, behavioral disorders, and a high social burden. Patients are usually classified at admission for detoxification treatment according to the decision tree developed in 1990 (Lesch et al., 1990). If it is not possible to determine an appropriate medical history at admission, a time period of 5 days is allowed before classification into the referring type.

Lesch’s typology has been used in many research projects focusing on very different aspects of alcoholism research. This review will try to give an overview of the recent findings focusing on neurobiological aspects and treatment implications regarding the subtypes of Lesch’s typology.

Homocysteine and the glutamate system

Various recent studies have shown that elevated serum levels of the sulfur-containing amino acid homocysteine play a crucial role in the neurobiology of alcoholism (Bleich et al., 2005), particularly regarding withdrawal symptoms such as seizures (Bleich et al., 2000a, 2006), cognitive impairment (Wilhelm et al., 2006), and brain atrophy (Bleich et al., 2000b, 2003a). Homocysteine is an excitatory amino acid and leads to an increase of glutamatergic neurotransmission via overstimulation of NMDA receptors (Bleich et al., 2003b, 2004b; Bigal et al., 2007).

Regarding Lesch’s typology, it is known that patients of Lesch type 1 tend to suffer from seizures and more prominent withdrawal symptoms than patients of other types of Lesch’s typology. In a recent study, it has been shown that homocysteine serum levels are elevated in patients of Lesch’s type 1, especially in patients with a history of alcohol withdrawal seizures (Bleich et al., 2004a). As homocysteine acts as a glutamate agonist at the NMDA receptor, it is interesting whether there are differences regarding serum levels of glutamic acid between the different types of Lesch’s typology. In a recently published work Walter et al. showed that blood levels of glutamic acid differ between patients of Lesch’s typology. In this study, the authors investigated a sample of 159 alcoholics, measuring glutamic acid in peripheral blood and assessing the type of alcohol dependence according to Lesch’s typology. As a main finding, patients of types 1 and 4 showed significantly higher levels of glutamic acid than patients of types 2 and 3. The authors interpret these findings in type 1 patients as a “kindling” phenomenon while in type 4 patients elevated glutamic acid values may be related either to compulsivity and/or to the frequent repetition of drinking and withdrawal (Walter et al., 2006).

Taken together, these findings show that particularly patients of Lesch’s type 1 and possibly patients of type 4 seem to suffer from changes in glutamatergic pathways which might underline the marked withdrawal symptoms in these groups.

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Genetics and Lesch’s typology

Many different candidate gene polymorphisms have been identified which may be associated with alcoholism or with specific features of the disease (e.g., withdrawal seizures). However, most of these reports did not include subtyping of alcohol patients. Most recently, a first study investigated Lesch’s typology in respect to genetic investigations (Bönsch et al., 2006). Bönsch et al. investigated a sample of 134 alcoholics admitted for detoxification treatment with respect to different MTHFR (methylene-tetrahydrofolate reductase) genotypes. MTHFR is of crucial importance in the homocysteine pathway, acting as a carbon donor in the remethylation of homocysteine to methionine. Findings of this study revealed a significantly higher frequency of the thermolabile MTHFR (C677T) variant in patients of Lesch’s type 4 compared to type 2 and 3 patients. This first study points towards a genetic determination of Lesch’s typology.

Another recent study that focused on genetic variants in different subgroups of Lesch’s typology found no evidence for a role of different polymorphisms in patients of Lesch’s types 1 and 2 (Samochowiec et al., 2008). This investigation included the dopamine transporter (DAT), the D2 receptor (DRD2), the serotonin transporter (5HTT), and the catechol-O-methyltransferase (COMT) polymorphism. However, this study could not provide any results regarding Lesch’s type 3 and 4 patients as the number of included subjects was too small for analysis. In conclusion, this second study shows that further studies including larger numbers of patients are necessary to verify these first results and to investigate other candidate genes in respect to different subtypes of Lesch’s typology.

Neuroendocrinological findings

Endocrinological changes have particularly been associated with alcohol craving, including changes of the hypothalamic-pituitary-adrenocortical axis (HPA-axis), changes of appetite regulating peptides, and other hormones associated with stress response and dopaminergic neurotransmission.

Several studies have shown that the HPA-axis is disturbed during active drinking, withdrawal, and abstinence (Kiefer et al., 2002b; Kiefer and Wiedemann, 2004). For example, decreased CRH (corticotropin releasing hormone) is associated with elevated craving in alcohol dependence (Fahlke et al., 1994; Olive et al., 2003). Furthermore, studies found low cortisol and ACTH (adrenocorticotropic hormone) serum levels to be associated with increased craving and higher relapse rates (Kiefer et al., 2002b; Junghanns et al., 2003).

Also, other endocrinological changes have been described in alcoholism. Prolactin secretion is closely connected to dopaminergic transmission, reflecting changes of the tuberoinfundibular dopamine pathway. Furthermore, prolactin is known to be elevated in stress situations. A recent study investigated possible associations between prolactin serum levels and alcohol craving during alcohol withdrawal differentiating alcohol-dependent patients using Lesch’s typology (Hillemacher et al., 2006b). This study assessed 115 male patients suffering from alcohol dependence according to ICD-10 criteria with the Obsessive Compulsive Drinking Scale (OCDS) during early alcohol withdrawal. Results revealed a significant association between prolactin serum levels and extent of craving measured by the OCDS particularly in Lesch’s type 2 patients. This is interesting because patients of Lesch’s type 2 are characterized to suffer from anxiety and to use alcohol because of its anxiolytic effects. Anxiety disorders are also known to be associated with elevated stress levels and prolactin elevation (Hollander et al., 1989; Apostolopoulou et al., 1993). This finding may therefore reflect a shared pathophysiological pathway between anxiety disorder and alcohol craving in patients of Lesch’s type 2.

Another important neuroendocrinological pathway in the pathogenesis of alcohol craving seems to be the appetite-regulating system. In this context the endocrinological peptides leptin and ghrelin have received most attention. Kiefer et al. firstly described that increased plasma concentrations of leptin may be associated with increased subjective rates of alcohol craving (Kiefer et al., 2001a, 2001b). Other studies showed that leptin plasma concentrations were elevated during chronic alcohol consumption (Nicolas et al., 2001), normalized during withdrawal and abstinence (Wurst et al., 2003). Using a large study sample a recent investigation provided evidence that leptin serum levels are associated with the extent of alcohol craving during early alcohol withdrawal (Hillemacher et al., 2007a). Also, the gastrointestinal peptide ghrelin was shown to be increased in alcohol dependence. Kim et al. found higher ghrelin levels in alcohol abstainers and a positive association with the duration of abstinence (Kim et al., 2005). Other studies described an involvement of ghrelin in the brain reward systems in an animal-experimental study (Jerhagh et al., 2006). A recent investigation described ghrelin levels to be elevated during alcohol withdrawal. However, this study found no association between ghrelin serum levels and alcohol craving (Kraus et al., 2005). In contrast to these findings, another recent investigation from Addolorato and colleagues found significantly lower plasma ghrelin levels in alcoholics and a significant relationship between ghrelin levels and alcohol craving scores (Addolorato et al., 2006).

A recent investigation analyzed the role of these peptides in alcohol craving in respect to Lesch’s typology (Hillemacher et al., 2007b). This investigation was based on a sample of 188 patients with alcohol dependence, admitted for alcohol detoxification. Craving was measured using the OCDS. Using general linear models the authors found a significant positive association for leptin in patients of Lesch’s types 1 and 2, while ghrelin showed a trend regarding an association with craving in patients of Lesch’s type 1. These findings show that appetite-regulating peptides which obviously play an important role in alcohol craving may be of special interest in particular subtypes of patients.

Volume regulating mechanisms and alcohol craving

Other studies focused on differences regarding the association of drinking behavior and alcohol craving between subtypes of Lesch’s typology. Different studies have indicated a beverage-dependent influence on craving apart from the association with alcohol intake itself.

Consumption of low alcoholic drinks such as so-called alcohol free beer was found to be associated with increased craving (Long and Cohen, 1989). A recent study found that craving is not only associated with alcohol intake itself but also with the type of consumed alcoholic beverage (Hillemacher et al., 2005). Furthermore, changes in volume-regulating peptides during alcohol intoxication and withdrawal were described recently in various studies (Eisenhofer et al., 1985;
The “kindling” effect and other important findings

A recent study showed that recurrent detoxifications are associated with elevated alcohol craving (Malcolm et al., 2000), reflecting a “kindling” effect which has also been associated with the elevated risk of alcohol-related seizures after multiple detoxifications (Lecenstein and Worner, 1991; Becker and Hale, 1993; Anton et al., 1996; Worner, 1996; Boothby and Doering, 2005). However, other investigations found contradictory results (Duka et al., 2002).

A recent study investigated a large patients sample regarding the role of recurrent detoxifications in alcohol craving in respect to the subtyping of Lesch (Hillemacher et al., 2006a). This study examined a sample of 192 patients, using the OCDS to assess the extent of craving during early alcohol withdrawal. Regarding a possible association between the number of previous detoxifications and alcohol craving, findings show a significant correlation for the whole population but particularly for patients of Lesch’s type 1. This suggests that the kindling effect may be particularly important in a subgroup of patients. These findings may also help to interpret the previous contradictory findings and underline the importance of subtyping patients with alcohol dependence.

Another interesting concept investigated was the concept of abnormal hemispheric organization in alcoholism. This concept was studied previously in the area of endogenous psychosis and focuses on the frequency of left-handedness (Sperling et al., 2000). In a sample of 250 alcoholic inpatients, Sperling et al. found a significantly higher frequency of left-handedness in type 4 patients of Lesch’s typology. According to the authors, left-handedness and therefore abnormal hemispheric organization may be a sign of the cerebral damage which is a characteristic of type 4 patients.

Association with nicotine dependence

Many studies document the well-known association between alcohol and nicotine dependence. Epidemiological investigations found a consistent association between alcohol and nicotine consumption (Zacny, 1990). A recent investigation demonstrated that in alcohol-dependent patients obsessive-compulsive craving is associated with the extent of nicotine dependence (Hillemacher et al., 2006c). We further analyzed these data, comparing patients regarding Lesch’s typology of alcohol dependence. The severity of nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND) (Fagerström et al., 1990; Heatherton et al., 1991), and the extent of alcohol craving was measured using the OCDS (Anton et al., 1996). All patients included in the study suffered from alcohol dependence according to DSM-IV and were assessed after admittance to the detoxification unit. Findings of the Spearman’s correlation analysis revealed significant associations particularly in patients of Lesch’s type 2 (OCDS total score: \( r = 0.274, P = 0.045, N = 54 \); OCDS compulsive subscale: \( r = 0.319, P = 0.019 \)) and of Lesch’s type 4 (OCDS total score: \( r = 0.527, P = 0.20; N = 19 \); OCDS compulsive subscale: \( r = 0.472, P = 0.041 \)). We found no significant associations for Lesch’s type 1 (\( N = 27 \)) and Lesch’s type 3 patients (\( N = 22 \)). Also, no significant correlations with the obsessive subscale of the OCDS could be observed. In conclusion, these findings show that the subtyping of patients with alcohol dependence is also important when investigating associations with other comorbidities like nicotine dependence. Differences in brain pathophysiology between specific patients’ groups—particularly in the prefrontal and the orbitofrontal cortex—may help to explain these results as these circuits have been associated with compulsive behavior and drug use which may be the link between nicotine dependence and alcohol craving (Volkow et al., 1999; George et al., 2001; Grüsser et al., 2004). The current findings should lead to further investigations regarding the involvement of these circuits in specific patient groups, which may also be of importance for differential treatment strategies.

Implications for therapy

Various studies have investigated different treatment options in respect to Lesch’s typology. The United Kingdom Multicentre Acamprosate Study (UKMAS) found no differences in the response to acamprosate regarding Lesch’s typology (Chick et al., 2000). However, in this study patients of types 3 and 4 were overrepresented. In the Austrian Acamprosate trial results show a better response to acamprosate in patients of types 1 and 2 (Lesch et al., 2001). Kiefer et al. found that acamprosate was particularly efficacious in patients of Lesch’s type 1 while naltrexone was more effective in type 3 and type 4 patients (Kiefer et al., 2005). Also studies on other agents like flupenthixol have been performed. In a large study it was shown that flupenthixol is not only beneficial but also increases relapse rates in abstinent patients (Wiesbeck et al., 2001). In respect to Lesch’s typology, Walter et al. showed that flupenthixol has this detrimental effect only in patients of types 1 and 3 (Walter et al., 2001). These findings demonstrate that different types of alcohol-dependent patients do respond to pharmacological interventions in a distinct manner, which should be considered when treating patients with antitocraving substances such as acamprosate or naltrexone. Furthermore, a specific subtyping is useful when investigating new treatment options for relapse prevention, such as topiramate or bupropion (Addolorato et al., 2002; Johnson et al., 2003).
CONCLUSION

The presented findings may lead to two important conclusions. The different studies focusing on very different aspects in alcoholism show that the Lesch typology has a biological and genetic basis (see Fig. 1). Furthermore, dividing patients into subgroups has an important impact for further research strategies as completely different findings might be found regarding neurobiological mechanisms as well as the efficacy of pharmacological treatment. Testing new pharmacological options and psychotherapeutical or psychosocial interventions, it is important to take into account that these may have different efficacy when used in patients of different subgroups. Of course, also other typologies are of high interest in research and therapy (Babor and Caetano, 2006). A recent analysis comparing different typologies of alcohol dependence supports the concept of four homogeneous types of alcoholism (Hesselbrock and Hesselbrock, 2006). Therefore, Lesch’s typology offers a good basis for research and for a better understanding of alcoholism. Further investigations (e.g., a large European multicenter study) should be performed to assess whether Lesch’s subtypes of alcoholism are associated with specific electrophysiological, neuroendocrine, genetic, and cognitive markers to confirm that this typology may be useful to define endophenotypes of alcoholism. Approaches for specific typologies are also necessary in other areas of addiction such as nicotine dependence (Lesch et al., 2004).

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