Biological vulnerability to alcoholism in children of alcoholics

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General discussion

Introduction
Alcoholism is a multifactorial disease, with interactions of polygenic and environmental influences (Goodwin et al., 1973; Cloninger, 1981; Goldman, 1995). The heritability of the genetic component of alcoholism risk has been estimated as ranging from 50-60% (Heath et al., 1997). To gain knowledge about what is inherited in alcoholism, it is useful to study trait markers, because trait markers for alcoholism are defined as: (1) themselves heritable: as twin studies and adoption studies have assessed, variations in the trait marker are largely based on genetic factors as opposed to environmental factors; (2) more prevalent in alcoholics than in unrelated non-alcoholics; and (3) state independent, not reflecting the current state of alcoholism but present during an individual’s lifetime, as can be assessed in high risk subjects such as children of alcoholics (COA) (Eskay & Linnoila, 1991; Hill et al., 1991; Sher et al., 1991). In addition, to prevent false positive conclusions based on population stratification, the marker should co-segregate with alcoholism within families, as can be shown by sib pair analyses, or other genetic analyses of pedigree data (Begleiter & Porjesz, 1988). In the study of alcoholism, a trait marker is a pathophysiological marker that increases knowledge about the aetiology of the clinical condition; it does not necessarily have a high sensitivity and high specificity for the clinical condition itself, as a diagnostic marker would (Begleiter & Porjesz, 1988; Nurnberger, 1992). A risk factor is only associated with the clinical condition. Further investigations are needed to address whether the risk factor fulfils the criteria of a trait marker. In this thesis two populations were studied in three chapters, apart from the review presented in chapter

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The first project presented in chapter two and three, aimed at studying young children of alcoholics. The second project presented in chapter four aimed at studying non-alcoholic young adult children of alcoholics. This general discussion provides an overview of both projects in relation to the outcomes of the review, aiming to present recommendations for further studies.

The Relevance of Trait Markers and Risk Factors

In the last decade, studies on trait markers for alcoholism have focused on behavioral, psychophysiological, and neurochemical trait markers for alcoholism (Begleiter & Porjesz, 1988; Farren & Tipton, 1999; Schuckitt, 1999; Van der Stelt, 1999; Tabakoff et al., 2001). In the present thesis, the possible biochemical trait marker adenylyl cyclase, the probable psychophysiological trait marker P3, and two risk factors for alcoholism were studied. The two risk factors were (1) a polymorphism of the dopamine D2 receptor gene, which may be related to a functional mutation of this receptor and to severe alcoholism (Noble, 1996); and (2) increased sensation-seeking behavior (Bardo et al., 1996; Cloninger et al., 1988). In the present thesis these possible trait markers and both risk factors were studied, in two projects: (1) in order to investigate the state independence of this trait marker, the presence of a reduced stimulated adenylyl cyclase activity was assessed in platelets of COA; and (2) in order to investigate whether these three characteristics together represented one risk factor for alcoholism, the relationship between the probable trait marker P3 and two risk factors for alcoholism in ACOA was assessed.

In the first project, the assessment of the state independence of adenylyl cyclase activity is in accordance with other studies that have
investigated the state independence of a possible trait marker in a population of high risk children for alcoholism (Schuckit et al., 1983; Schuckit & Gold, 1988; Stelt et al., 1998; Twitchell et al., 1998). The previous studies on adenylyl cyclase activity focused either on the direct stimulation of the adenylyl cyclase or the indirect stimulation of adenylyl cyclase by the G-protein activity (Tabakoff et al., 1988; Hoffman & Tabakoff, 1990; Devor et al., 1991; Saito et al., 1994; Parsian et al., 1996). To our knowledge no earlier study has been made of both directly and indirectly stimulated adenylyl cyclase activity within one study of the children of alcoholics and control children.

The second project of the thesis investigates the P3, the presence of the A1 allele as a polymorphism of the dopamine D2 receptor gene, and sensation seeking, to assess whether these three characteristics represent a single risk factor within a group of adult children of alcoholics. Risk factors for alcoholism will be more frequently present in high-risk children than in controls, and possible existing relations will be easier to find. Sensation-seeking, especially, is at its peak during young adulthood. This is why young non-alcoholic adult children of alcoholics were studied. The aim of studying the relations between the probable trait marker P3 and both risk factors as one risk factor for alcoholism has not, to our knowledge, yet been raised in other studies. On the contrary, it has been investigated whether the P3 is strictly related to dopaminergic dysfunctions (Noble et al., 1994, Hill et al., 1998).

The present thesis also aimed to describe the presence of (co-morbid) psychopathology in alcoholics and in their children. The presence of psychopathology can be seen as a nuisance variable that has to be controlled for in COAs or excluded from the study population if present in alcoholic

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parents (Schuckitt, 1989; Hill et al., 1999). However, psychopathology has also been used in other studies as a risk factor for alcoholism in later life (Reich et al., 1993; Kuperman et al., 1999; Kushner et al., 1999). In the present thesis psychopathology was studied in both ways: (1) as a nuisance variable, a covariate that one might have to control for, in the study on adenylyl cyclase activity in COA; and (2) as a possible risk factor for alcoholism in later life, present in COA, studied in relation to parental alcoholism, co-morbid psychopathology in the alcoholic parent, the number of alcoholic parents (one or two), gender, and a family history of alcoholism.

Finally, another aim of the present thesis was to review studies of indices of changes within five neurotransmitter systems that were hypothesized to be involved in alcoholism vulnerability in humans. They comprised: GABA (Koob et al., 1986; Frye & Breese, 1982), serotonin (Cloninger, 1987; Linnoila et al., 1983), dopamine (Gessa et al., 1985; Imperato & Di Chiara, 1986; Wise & Bozarth, 1987), norepinephrine (Cloninger, 1994), and β-endorphin (Blum, 1983; Reid et al., 1984; Hubbel et al., 1986). This was done to report whether these changes fulfilled the criteria of a trait marker, and whether they related to the presence of a vulnerability to develop alcoholism within humans, or whether these changes can only be understood as state dependent changes, present after the use of alcohol that itself influences the activity within neurotransmitter systems (Nestler, 1999; Saito & Tabakoff, 1985). A review on possible neurochemical trait markers has recently been performed (Farren & Tipton, 1999). However, to gain knowledge about what trait marker criteria might be necessary to investigate in further studies, the present review not only reports the studies of possible neurochemical trait markers in alcoholics but
consequently reports the studies made of COA and the studies made of heritability aspects.

**Methods and Subjects**
Alcoholics who voluntarily seek help more frequently exhibit psychopathology, and suffer more severe alcoholism, than do alcoholics who do not seek help (Helzer & Pryzbeck, 1988; Treu et al., 1996). It may be assumed that alcoholic parents without psychopathology, or parents with externalising psychopathology, might seek help less often than do parents with internalizing psychopathology such as anxiety or depression. Among the 39 alcoholic parents who were included in the present thesis, 78% had at least one co-morbid DSM-III-R disorder, mainly mood and anxiety disorders. Among the COA, 50% had at least one DSM-III-R disorder, mainly depression and anxiety disorders. As our aim was to describe the influence exerted by parental psychiatric co-morbidity, the number of alcoholic parents (one or two), gender and a family history of alcoholism on psychopathology in COA, the substantial presence of psychopathology in our subjects was fortunate. Although the results of this study cannot be generalized to all children of alcoholics, they may nevertheless assist professionals working in addiction centers to better understand the risk for psychopathology in the children of their alcoholic clients seeking help.

Koot et al. (1999) has shown that low SES is an important risk factor for the development of psychopathology in Dutch children. The presence of psychopathology in children from families with low SES, and the development of alcoholism in later life might be one risk factor; by excluding subjects with low SES from the study population, it may thereby be deprived of high risk subjects, and the investigated relationship in COA,
for example, between externalising psychopathology and a family history of alcoholism might not be found (Schuckit, et al., 2000). The influence of SES was therefore carefully assessed in the present thesis, and in COA it was found that low SES was of influence on the presence of DSM-III-R psychopathology. SES was therefore used as an important covariable in the present study (Chapter 2).

Results

The result of the first project of a lower stimulated adenylyl cyclase activity shown in COA than in controls was expected. Importantly, this result was based on a reduction in fluoride-stimulated G-protein activity, and not by direct stimulation of adenylyl cyclase by forskolin. Remarkably, a fluoride-stimulated reduced activity of almost 50% in multigenerational COA as compared to unigenerational COA, equaling control values, corroborates the study of Devor et al. (1991). They reported a Mendelian major gene effect with multifactorial background of the reduced fluoride-stimulated G-protein activity in alcoholism. Saito et al. (1994) also reported lower G-protein activity in alcoholics with a positive family history of alcoholism than in alcoholics without alcoholism in their families. The present results were gender-independent and also in agreement with Lex et al. (1993), reporting a lower adenylyl cyclase activity in family history-positive non-alcoholic women, relative to family history-negative non-alcoholic women. Finally, the present results corroborated the findings of the WHO/ISBRA Collaborative study which reported a large effect of fluoride stimulation and a smaller effect of forskolin stimulation of adenylyl cyclase activity in alcoholics relative to controls (Menninger et al., 2000). The amount of Gs-protein expression has a marked impact on the level of activity of adenylyl
cyclase (Yang et al., 1997). High risk subjects had higher levels of Gs-protein expression than did low risk subjects in erythrocyte membranes (Wand et al., 1994). The question arises which tissues with changed Gs-protein expression, especially changes within neurotransmitter systems, may be related to vulnerability for alcoholism.

The results of the second project showed that the three characteristics did not together represent a common risk factor. The relation between increased sensation-seeking behavior and a lower P3 amplitude was expected, and corroborates with other studies indicating that increased externalising behavior is a possible moderator between a low P3 amplitude and the development of alcoholism (Branchey et al., 1988; Bauer & Hesselbrock, 1999; Carlson et al., 1999; Van der Stelt et al., 1998).

The finding of increased internalizing psychopathology in the daughters of alcoholic mothers has been reported in another study (Christensen & Bilenberg, 2000). However, a cross-gender effect has also been reported, of increased psychopathology in the daughters of alcoholic fathers (Hill et al., 1999). The exclusion of subjects with co-morbid psychopathology in the latter study may explain the differences between the studies, as our study and that of Christensen and Bilenberg (2000) did not exclude parents with co-morbid psychopathology, which influences psychopathology in the child, from the sample. Although it was expected to find increased internalizing psychopathology in the COA population based on the inclusion criteria of the parents, the gender effect of alcoholic problems in mothers on internalizing psychopathology in their daughters cannot be explained by the inclusion criteria of the study.

Reviewing the changes in five neurotransmitter systems, it was found that an increased serotonin transporter activity may be a trait marker
for alcoholism. Serotonin dysfunction has been related to alcoholism, and most consistently to impulsive aggression (Cloninger, 1987; Linnoila et al., 1983). Although our review reports increased serotonin transporter activity as a possible trait marker for alcoholism, it might also be the case that behavioral dysregulation is more closely related to serotonergic dysfunction than to alcoholism risk, as Twitchell et al. (1998) has reported that behavioral dysregulation in COAs was more closely connected to serotonergic function than to paternal alcoholism. By the same token, although a low P3 might be more closely connected to increased externalizing behavior than to alcoholism, externalizing behavior might itself increase alcoholism risk.

*Current Issues*

Earlier studies have held that primary alcoholism, anxiety and depression, and to the same extent primary alcoholism and antisocial personality disorder, were separate disorders that congregated in different families (Schuckit, 1973; Cloninger et al., 1983), and that secondary alcoholism might develop after a depression or an antisocial personality disorder had occurred (Schuckit, 1989). More recently it has been shown that the family factors underlying depression and alcohol abuse are substantially intercorrelated, and that the family factors underlying antisocial behavior and depression are significantly intercorrelated in a pedigree analysis (Stallings et al., 1997). In a prospective longitudinal study (Kushner et al., 1999), alcohol dependence and anxiety disorders also show a reciprocal causal relationship over time. It may be concluded that the risk for alcoholism appears not to be based on a separate pathophysiological process, as could be understood by the term ‘primary’ as opposed to ‘secondary’
alcoholism, but that co-morbid disorders in alcoholism, such as alcohol dependence and anxiety, may have a single pathophysiological process in common.

**Recommendations**

The present findings have indicated that a risk factor such as sensation-seeking behavior and the probable trait marker P3 are related (Chapter 4). Other studies have shown that the P3 may be a trait marker for alcoholism (Porjesz et al., 1998; Van der Stelt et al., 1998; Van der Stelt, 1999). The extremes of externalising behavioral dysfunction may be an important moderator between a low P3 and the development of alcoholism (Chapter 4). The aggressive behavior syndrome scored by the CBCL had heritabilities ranging from 0.52 to 0.94 (Achenbach, 1999) and had a long-term stability (Stanger et al., 1997). This syndrome score may be a valid and reliable variable to measure externalizing behavioral dysfunction, because it may fulfil the criteria for a trait marker for alcoholism.

Risk factors may signify developing alcoholism, and the use of multiple tests on risk for alcoholism in an individual may allow discrimination between a high risk and a low risk individual (Schuckit & Gold, 1988; Reich et al., 1993). In order to report whether the trait markers signify the risk of alcoholism in later life, and to report whether they add up differently between high risk and low risk children, it is recommended to investigate the presence of several trait markers within young children at risk of developing alcoholism in later life. This study will not directly benefit the included children, in the sense that it will not deliver a diagnostic test. The study will, however, reveal some part of the pathophysiological mechanism of alcoholism.
In the present thesis, reduced stimulated adenylyl cyclase activity was present in COA as a trait marker (Chapter 3). This effect in adenylyl cyclase may be masked in alcoholics by the use of alcohol (Menninger et al., 1998), to the extent that it was argued that this masking effect in alcoholics may be present with the reported increased serotonin transporter activity in COA (Chapter 1). It may be useful to study the change of the stimulated adenylyl cyclase activity during the development of alcoholism within an individual, and to report whether a masking effect of alcohol is present. This masking effect may explain how unexpected changes of trait marker activity within alcoholics may occur.

It is recommended that in a future study, externalizing behavioral dysfunction, together with possible separate trait markers such as decreased stimulated adenylyl cyclase and the P3, are assessed in a follow-up design which includes high risk children and controls, assessing the development of alcoholism as the outcome variable. This study would have three aims: (1) to discover whether the same relations are found between trait markers and externalizing behavioral dysfunction in both groups or whether different relations are found, since this will help us to understand more about the possible moderating effects of externalizing aggressive behavior on the risk for alcoholism; (2) to study whether the two trait markers and externalizing behavioral dysfunction may be of significance during the development of alcoholism; and (3) to illuminate how trait markers may be masked over time by the use of alcohol after alcoholism has developed.