Biological vulnerability to alcoholism in children of alcoholics

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Summary

Both an individual’s genes and their environment are involved in the development of alcoholism. Furthermore, the roles of these two factors interact. The pathophysiology of alcoholism deals with inherited pathophysiologic abnormalities that may cause an individual to become an alcoholic. When taking this approach, one has to take into account both an individual’s genes and their environment. The present thesis represents an attempt to increase our understanding of the pathophysiology behind the development of alcoholism. Trait markers or vulnerability markers were studied, because these are the characteristics of an individual that represent a genetic risk of alcoholism. This biological vulnerability to alcoholism may even be present in young children. Thus trait markers are present in an individual long before a disorder, an illness or symptoms have developed.

The biological vulnerability for alcoholism was investigated in this thesis in four chapters: (1) a review on three trait marker criteria for alcoholism of changes within five neurotransmitters systems; (2) a study on the presence of psychopathology, a risk factor for alcoholism, in young children of alcoholics (COA); (3) a study on the state independence of a lower stimulated adenylyl cyclase activity in platelets from children of alcoholics; and (4) a study on the relationships of three characteristics of increased risk for alcoholism, a lower P3 amplitude, the presence of the A1 allele of the dopamine D2 receptor gene and increased sensation seeking behavior in a study of young adult children of alcoholics.
Chapter one

The first chapter addresses three trait marker criteria of indices of changes within five neurotransmitter systems. Animal studies have shown that alcohol produces reinforcing effects, by acting on several neurotransmitter systems, and activating the reward system of the brain. Potential trait markers for alcoholism of neurochemical origin have been studied in alcoholics and children of alcoholics. Indices of changes in five neurotransmitter systems, GABA, serotonin, dopamine, norepinephrine and \( \beta \)-endorphin have been implicated to play an important role in alcoholism, and have been reviewed as trait markers for alcoholism according to three criteria: (1) to be present in alcoholics as compared to unrelated non alcoholics; (2) to be present in COA; and (3) to be heritable. Baseline, challenge studies and post-mortem studies are reported.

It can be argued from the GABA challenge studies that the measurement of decreased responsiveness in GABA neurotransmission fulfils two criteria for a trait marker, it is present in alcoholics and in COA. Further studies on the heritability are needed. The measurement of decreases within the baseline GABA neurotransmission fulfils two criteria, it is heritable and present in alcoholics and must be further studied in children of alcoholics to assess the state independence of the decreases. The studies on serotonin activity have shown that an increase in serotonin transporter activity, fulfils all three reviewed criteria, but may possibly be masked by the recently use of alcohol, that leads to a decrease of the serotonin transporter activity in active and shortly abstinent alcoholics. This may possibly also holds true for the presence of a decreased postsynaptic serotonin receptor response in alcoholics versus an increased response in COA, using challenge studies, indicating that these decreases fulfil at least
one criterium. The challenge and baseline studies of dopamine activity in alcoholics have shown contradictory results, however indices of decreased receptor reactivity were found in long-term abstinent alcoholics fulfilling one criterium. Studies in the norepinephrine system, showed measurements of decreases of norepinephrine baseline levels, and decreases of postsynaptic $\alpha_2$ adrenergic receptor reactivity in alcoholics. The baseline and challenge studies, both fulfil one criterium, to be present in alcoholics. More studies, on the presence of these decreases in COA and on the heritability, are needed. The decreased baseline level of $\beta$-endorphin in alcoholics and COA, fulfilling two criteria, with an increased $\beta$-endorphin response to alcohol and naloxone in alcoholics and COA, are findings that might be consistent with the opioid deficiency hypothesis. The finding that inter-individual differences in challenged $\beta$-endorphin levels are heritable suggests the possibility that increased responsiveness of the $\beta$-endorphin system may be a trait marker for alcoholism, as it seems to fulfil all three investigated criteria.

In conclusion, two possible neurochemical markers fulfilled the three investigated criteria for a trait marker, to be heritable, to be present in alcoholics and to be present in COA: (a) measurements of an increased basal activity of the serotonin transporter; and (b) measurements of increased responsiveness of the pituitary $\beta$-endorphin system after challenges. Regarding the neurochemical vulnerability for alcoholism, arguments are presented to underline the necessity of studying trait marker properties in individuals at risk for alcoholism.
Chapter two

In the second chapter, the psychopathology was described that was present in the children of parents seeking treatment for their alcoholism. In addition, it was investigated whether gender, parental psychiatric co-morbidity, number of alcoholic parents, and family history of alcoholism, were related to psychopathology in the children of treatment seeking alcoholics (COA). Parental alcoholism is associated with both externalising psychopathology (conduct disorder, oppositional disorder, attention-deficit hyperactivity disorder, alcohol and substance abuse) and internalising psychopathology (major depressive episodes, several anxiety disorders) in their offspring. The nature and the extend of these relationships seems to be dependent on the gender of the alcoholic parent, the gender of the COA, the presence of co-morbid psychopathology in the alcoholic parent, the number of alcoholic parents and the existence of a multigenerational family history of alcoholism. The question arises whether psychopathology in children at risk of alcoholism is related to a positive family history of alcoholism (defined as the presence of a multigenerational rather than an unigenerational family history of alcoholism) or whether it is related to other parental effects (related to the number of alcoholic parents, their gender, and any parental psychiatric co-morbidity). Because low socio-economic status (SES) in parents is a well known risk factor for the presence of psychopathology in their offspring, the influence of SES on psychopathology in COA was also assessed.

The study had two aims. One is to describe any psychopathology present in male and female COA (using DSM-III-R diagnostic criteria) whose parents are seeking treatment for alcoholism. The other objective is to determine whether gender, parental psychiatric co-morbidity, the number of
alcoholic parents and a positive family history of alcoholism are related to DSM-III-R psychopathology in COA. The sample consisted of 60 COA (28 boys, 32 girls) aged 7 to 18, from 39 families. These families included 39 alcoholic index parents (16 mothers, 23 fathers) under treatment for their alcoholism, of whom 9 had spouses who were also alcoholics (1 mother, 8 fathers). DSM-III-R diagnoses were assessed in COA and in index parents. Among the 39 alcoholic index parents, 78% had at least one co-morbid DSM-III-R disorder, mainly affective and anxiety disorders. Among the COA, 50% had at least one DSM-III-R disorder mainly depression and anxiety disorders. Depression and anxiety disorders were over-represented in the daughters of alcoholic mothers, who had an increased risk to have depression and anxiety disorders than other COA.

In conclusion, as expected, the gender of the alcoholic parent exerted an influence on the psychopathology of COA. This, however only occurred in the daughters of alcoholic mothers. They were seven times more likely to have depression and anxiety disorders than other COA. Unexpectedly, parental psychiatric co-morbidity, the number of alcoholic parents, and family history status did not predict psychopathology in COA.

Chapter three

In the third chapter, the presence of a lower stimulated adenylyl cyclase activity was: (1) compared between COA and control children; and (2) related to the presence of a multigenerational family history of alcoholism in children of alcoholics. The most promising biochemical trait marker seems to be a reduced guanine nucleotide binding (G$_s$) protein stimulated adenylyl cyclase activity in platelets and lymphocytes in alcoholics. Unfortunately, a major shortcoming
of these studies is that the observed difference in platelet adenylyl cyclase activity between the adult alcoholics and controls may well be due to persistent changes in blood cells as a consequence of high daily alcohol consumption. Before accepting platelet or lymphocyte adenylyl cyclase activity as a reliable trait marker, it is crucial to show its altered activity in alcohol-naïve persons with a high risk to develop alcoholism, such as children of families with multi-generational alcoholism. We investigated this phenomenon in platelets of children of alcoholics (COAs), i.e. of children at high risk for the acquisition of alcoholism and (as yet) not regularly consuming alcohol.

In platelet membranes of 23 (male and female) COAs and 20 control children were assessed: (1) Gs-protein mediated stimulation of adenylyl cyclase by 30 mM NaF; and (2) 50 iM forskolin stimulated adenylyl cyclase activity. Gs-protein stimulated cAMP production by NaF, unlike that induced by direct stimulation of adenylyl cyclase with forskolin, in platelet membranes of COAs was profoundly lower than in platelet membranes of control children. Moreover, such a reduced Gs-protein functioning was only observed in platelet membranes of COAs with a multigenerational family history of alcoholism. This result was not confounded by the psychopathology reported in this group of COAs in the second issue of this thesis.

In conclusion, a reduction of Gs-protein stimulated adenylyl cyclase activity in platelets may represent a sensitive and gender-independent trait marker for predisposition to alcoholism, rather than a state marker for alcoholism.
Chapter four

In the fourth chapter, the relationship was investigated between the P3, the A1 allele of the dopamine D2 receptor gene and sensation seeking behavior. Over the past two decades, evidence has accumulated indicating that the P300 or P3 component of the human event-related potential (ERP) may provide a vulnerability or trait marker of alcoholism, the P3 index a genetic risk factor in alcoholism. Dopaminergic neurotransmission may also play an important role in alcohol and drug abuse. Research has indicated a close relationship between the P3 event-related potential and the dopamine D2 receptor A1 allele in individuals at high risk for alcoholism. An association was reported in children between a prolonged latency and a small amplitude of the P3 and the presence of the A1 allele, a restriction fragment length polymorphism of the dopamine D2 receptor gene (DRD2); however, this a P3-DRD2 association was not found in data from the Collaborative Study on the Genetics of Alcoholism (COGA), though. In addition, dopaminergic neurotransmission may be involved in sensation and novelty seeking behavior which, in turn, has been associated with alcohol and drug abuse.

Participants, nonalcoholic adult children of alcoholics (n = 57; range 19-30 years; 41 females) performed a visual novelty oddball task to elicit the P3, were asked to fill in personality questionnaires including Zuckerman’s sensation seeking scale, and were classified according to the presence of the dopamine D2 receptor A1 allele. The relations between the P3, the A1 allele, and sensation seeking were assessed. The effects of gender, age and socioeconomic status (SES) were assessed to determine whether these variables affected the relations between the P3, the A1 allele, and sensation seeking. A small P3 amplitude was associated with high sensation seeking, particularly with high disinhibition. Disinhibition was associated with the
presence of the A1 allele, but only in men. By contrast, P3 amplitudes and latencies were not associated with the presence of the A1 allele.

In conclusion, although a small P3 amplitude, high sensation seeking and the presence of the A1 allele are all associated with alcoholism risk, the present findings indicate that these characteristics do not reflect a common risk factor in alcoholism.

General discussion

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.