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Mini Review

The Taq1a polymorphism of the dopamine D2 receptor gene – a key for understanding relapse proneness into alcoholism?

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Abstract

Alcohol use disorders (AUDs) are among the 10 leading causes of disability worldwide. Once an AUD is established, risk for relapsing within a year after treatment is very high. Repeated relapses further increase the risk of psychiatric and somatic co-morbidity, and alarmingly also for premature death (5-8 times higher compared to the general population). Oddly enough, there is still lacking knowledge of which individual traits that may predispose for elevated risk of repeated relapses. One such trait could be the Taq1A polymorphism of the dopamine D2 receptor (DRD2) and that individuals who are carriers of the so called A1 allele have fewer DRD2 and thus a genetically determined hypo-dopaminergic brain function. Knowledge of traits related to relapse proneness will improve the ability to provide tailor-made relapse prevention programs and thereby increase the effect-size of the treatment, and reduce psychological suffering, medical and psychiatric complications as well as premature death.

ABBREVIATIONS

AUD: Alcohol Use Disorder; **RDS:** Reward Deficiency Syndrome; **DRD2**: dopamine D2 receptor

INTRODUCTION

Alcoholism – one of the leading diseases worldwide

Let's start with some facts: Alcohol use disorder (AUD)is among the 10 leading causes of disability worldwide [1,2]. Once an AUD is established, risk for relapsing into drinking within a year after treatment is high (in the range of 65-70 percent) [2,3]. Repeated relapses increase the risk of psychiatric and somatic co-morbidity [4] and for premature death (5-8 times higher compared to the general population) [5,6]. Beside the individual consequences, AUDs also contribute extensively to violence with the family and to others.

It should be emphasized that the majority of individuals with AUDs are socially stable, i.e. having basic education, employment and permanent housing, even if having serious alcohol problems [7]. Thus, AUDs afflict a substantial part of the working population [8], meaning that it also negatively affects social inclusion, productivity and economic growth [9]. Oddly enough, there is still lacking knowledge of which individual traits that may predispose for elevated risk of repeated relapses and the subsequent consequences that follows thereof [10]. Knowledge of such traits will improve the ability to develop and provide tailor-made relapse prevention programs and thereby reduce psychological suffering, medical and psychiatric complications and premature death, and other problems such as sick leave and violence.

The dopamine D2 receptor – a disease modifier

One trait that appears to be a disease modifier and contribute to the severity of an individual's dependence is the gene for the dopamine D2 receptor (DRD2) [11,12]. In brief,DRD2 is an important contributor to the regulation of the brain reward circuitry – which is related to 1) "liking", hedonic feelings when doing things that we like, 2) "learning", learned predictions about what kind of stimulus that give hedonic feelings and 3) "wanting", incentive salience to reward relating stimulus [13]. When performing an activity that gives an individual pleasure, this activity will also reduce feelings of stress. Therefore, the DRD2 gene has been described not only as a reward gene but also as an "anti-stress" gene [13].

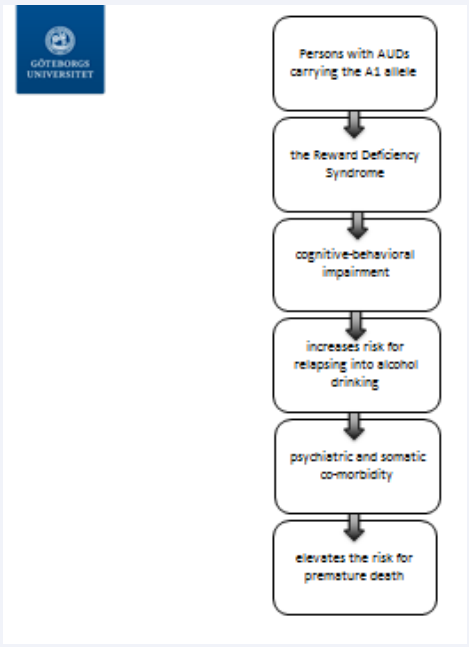

Figure 1 Hypothesized relationship between A1allele, relapse proneness and premature death.

The DRD2 gene contains several types of polymorphisms and one of them is the Taq1A polymorphisms. This polymorphism is usually presented in two variants where individuals can be designated either as "carriers of the A1 allele" or "non-carriers of this allele". About 30 % of the general population are carries of the A1 allele and among individuals with AUDs more than 40 % are carriers of this allele [5,12].

Presence of the A1 allele is related to hypo-dopaminergic brain function, i.e. low dopamine activity due to fewer dopamine D2 receptors [12,13]. Individuals with a hypo-dopaminergic function usually experience less hedonic feelings of natural rewards and have an impaired ability to cope with stress [13]. They are therefore more prone to seek unnatural rewards such as psychoactive drugs (e.g. alcohol), known to increase the dopamine activity in the brain [14]. Release of dopamine relieves temporarily the discomfort of stress and thus provides a "pseudo" sense of well-being. In fact, individuals with hypo-dopaminergic states consume in average more alcohol and drink more often with potential for heavy consumption relative with other excessive alcohol consumers [15]. Blum and colleagues [16] were the first to name this dopamine brain dysfunction as the "Reward Deficiency Syndrome" (RDS). According to Blum et al. [13], carriers of the A1 allele have a 74.4 % risk of developing RDS – which in turn can give rise to a variety of cognitive-behavioral difficulties that are directly associated with relapse proneness.

A theoretical model for relapse proneness

Taking the idea of RDS as starting point, a model for relapse proneness has recently been suggested by Balldin and colleagues [17]. The model is composed of studies that independently of each other have found a strong relationship between the A1 allele and AUDs. The model outlines why some individuals are more prone to continue relapsing, despite having received a standard psychosocial and/or pharmacological treatment for AUDs. It also outlines what the consequences will be if relapse is not prevented. The model is as follows:

More specific, carrying the A1 allele may strongly increase the risk for RDS as first stated by Blum et al [13,16] which in turn may affect a range of different cognitive-behavioral difficulties. For example, Young et al. [18] found that in a group of 56 medically ill and alcohol dependent patients the A1 allele was associated with lower self-reportedself-efficacy beliefs and less degree of self-reported confidence to abstain from alcohol in situations of social pressure such as "after work drinks". Connor et al. explored in a path analysis the relationship between age of problem drinking onset, dependence severity, alcohol expectancies, drinking refusal self-efficacy and A1 allele status in 143 alcohol-dependent inpatients [15]. Among others, the results indicated that in carriers of the A1 allele had earlier onset of problem drinking, and were more severely alcohol-dependent Furthermore, carrying the A1 allele and having an earlier onset of problem-drinking was related to lower drinking refusal self-efficacy. Other observed cognitive-behavioral characteristics among young healthy carriers of the A1 allele are, for example impaired impulse control [19] and reduced ability to cope with stress [13]. In addition, Jocham et al. [20] have demonstrated that in healthy carriers of the A1 allele have pronounced difficulties when tested in a so called reversal learning task. This computerized task means that the individual first learns to make discrimination, for example choosing a black object in a black/white discrimination problem, and then is supposed to learn to reverse his/her choice – i.e. to choose the white object.

The finding by Jocham et al. [20] is highly interesting since the core of treatment for addiction usually focus on how to behaviourally and emotionally handle daily situations without or with lesser amount alcohol. Thus, the majority of our today standard treatment for addiction contains strategies for how to revise an unhealthy behaviour and re-learn to use a healthy behaviour. This means that carriers of the A1 allele probably are disadvantaged since they cannot benefit from the treatment they are offered due to cognitive-behavioural deficits – i.e. instead of recovering, the risk of relapse into addiction increases. In fact, Dahlgren et al. [3] were the first to show that carriers of the A1 allele indeed are more prone to relapse after treatment for AUDs, compared to non-carriers of this allele (odds ratio: 7.1) [3].

As proposed in the model by Balldin et al. [17], relapse into drinking usually lead to a number of negative consequences, such as exacerbating psychiatric and somatic complications and also to premature death. Indeed, studies have shown that patients with AUDs carrying the A1 allele had been treated twice as often for such complications, compared to those who were non-carriers [4,12]. Interestingly, there are some studies showing that carriers of the A1 allele also tends to consume larger amounts of alcohol and have an earlier onset of problem drinking [15]. It seems therefore reasonable to assume that this severe drinking behavior, including relapse proneness, observed among carriers of the A1 allele, increases the risk for more medical complications and disorders, and also premature death. Indeed, Berggren and colleagues (2010) were first to show that the A1 allele is over-

represented among deceased patients with AUDs: they have a 10-fold increased risk of premature death compared to the general population [5]. Clearly, relapse proneness may have fatal effects, as well as for the victim as for relatives and ultimately for society. This strongly emphasizes the need to find specific psychotherapeutic methods for alcohol-dependent patients with cognitive-behavioral difficulties to abstain from alcohol – as those who are carrying the A1 allele.

With the proposed model of relapse proneness, as suggested by Balldin et al. [17] new interesting and challenging clinical research questions will arise. Central issues are, for example, if it is possible to find alternative cost-effective predictors of relapse proneness that can be used for matching an individual to a right type of psychosocial treatment. Other questions concern pharmacological treatments relevant to individuals with relapse proneness. For example, can potent dopamine receptor agonists, such as bromocriptine [21] or the dopamine stabilizer OSU6162 [22], reduce the risk of relapsing in combination with or without a tailored psychosocial relapse prevention program? The model can also contribute to theories related to stress-vulnerability, especially to the on-going epigenetic discussion. For example, it is suggested that the Reward Deficiency Syndrome (RDS) not only is involved in alcoholism, rather it seems to be a syndrome that can mediate other addictions problems such as smoking, gambling and excessive food consumption [11]. Moreover, there are evidence that (some) neuropsychiatric diseases also share abnormal reward sensitivity, maladaptive impulsivity or compulsive behaviors which can be reunited under the RDS' umbrella [23].

Tailored relapse prevention program are needed

In Sweden, the Swedish National Board of Health and Welfare [24] recommend that patients with AUDs should be treated with e.g. Cognitive Behavioral Therapy, the Minnesota Model, Motivational Enhancement Therapy or Psychodynamic Therapy since these methods have strong scientific support to be effective. These treatments are also today commonly used in outpatient treatment for addiction, but it should be emphasized that none of them includes treatment components that specifically meets the cognitive-behavioral shortcomings that characterize individuals who are at extreme high risk of relapse (e.g. carriers of the A1 allele). Moreover, research in the "recovery field", in general, has revealed poor outcomes in terms of relapse prevention and continued alcohol craving [25].

One assumption drawn from this discussion is that patients with the A1 allele probably would benefit from an add-on treatment to the today commonly used treatments, in which cognitive-behavioral difficulties are strengthened in order to refrain from alcohol. Thus, this raises the possibility that standard treatment is not enough for patients carrying the A1 allele – they need an add-on treatment focusing on their cognitive-behavioral shortcomings. Bearing in mind that AUD is one of the leading diseases worldwide [1,2] and relapse are among the greatest challenges facing those working in the field of addictions it is vital to meet the needs of developing effective treatment for alcoholism.

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