Chapter 4

Dopamine and Alcohol Dependence: From Bench to Clinic

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Additional information is available at the end of the chapter

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Abstract

Alcohol dependence, a chronic relapsing psychiatric disorder, is a major cause of mortality and morbidity. The role of dopamine in alcohol-induced reward as well in the development of alcohol dependence is reviewed herein. Both preclinical and clinical studies have suggested that alcohol activates the mesolimbic dopamine system (defined as a dopamine projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc, i.e. ventral striatum)) leading to a euphoric sensation. Alcohol dependence is characterized by a disruption in the reward-related brain areas including fewer dopamine D2 receptors in ventral striatum. Investigations of the underlying dopaminergic mechanisms involved during the development and maintenance of alcohol dependence could identify novel targets. Human and rodent experimental studies show that dopamine receptor antagonists, agonists and partial agonists as well as dopamine stabilizers influencing dopamine transmission, alter alcohol-mediated behaviours and thus may be potential treatment targets for alcohol dependence. Although there exists promising preclinical results, the majority of placebo-controlled randomized clinical trials with traditional dopamine antagonists and agonists have so far have been discouraging. Furthermore, the severe side-effect profiles of many of these compounds may limit their clinical use. Newer dopamine agents, such as partial agonists and dopamine stabilizers, attenuate alcohol-mediated behaviours in rodents as well as humans. Preclinical as well as clinical studies have shown that substances indirectly targeting the mesolimbic dopamine system may be potential targets for attenuation of alcohol reward. Collectively, the data reviewed herein may contribute to further understanding the complex mechanisms involved in development of alcohol dependence and we suggest that the newer dopamine agents as well as indirect modulators of dopamine signalling deserve to be further evaluated for treatment of alcohol dependence.

Keywords: alcohol-use disorder, mesocorticolimbic dopamine system, nucleus accumbens, dopamine stabilizer, antipsychotic drugs

1. Introduction

Alcohol dependence is a chronic relapsing psychiatric disorder significantly contributing to the global burden of disease [1] and affects about four percent of the world's population over the age of 15 (WHO). In the fifth edition of the diagnostic and statistical manual of mental disorders (DSM), the term alcohol use disorder was introduced and grossly defined as problem drinking that has become severe. The characteristics of this disorder include loss of control over alcohol intake, impaired cognitive functioning, negative social consequences, physical tolerance, withdrawal and craving for alcohol. To date, there are three medications approved by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of alcohol dependence; disulfiram, naltrexone and acamprosate. The FDA has also approved the use of a long-acting injectable naltrexone. More recently, the EMA granted authorization also for nalmefene, a compound intended for the reduction of alcohol consumption in adults with alcohol dependence (EMA 2012). Details regarding the mechanism of action of these compounds are outside the scope of this review. In brief, the pharmacological profile is established for disulfiram (an aldehydedehydrogenase inhibitor), naltrexone (an opioid receptor antagonist) and nalmefene (an opioid receptor modulator), whereas the mechanism of action of the anti-alcohol relapse drug acamprosate is not fully understood. An indirect activation of mesolimbic dopamine via accumbal glycine receptors and ventral tegmental nicotinic acetylcholine receptors (nAChRs) appears likely [2, 3], but additional targets has been suggested (for review see [4]). Finally, the clinical efficacy of these agents is limited [5], possibly due to the heterogeneous nature of the disorder and the complex neurochemical mechanisms underlying alcohol dependence. Thus, the need for novel and efficacious medications remains.

The mesocorticolimbic dopamine system (or the so-called brain reward system, **Figure 1**) is one of the established neurobiological systems involved during the development and maintenance of alcohol dependence and thus one potential treatment target. Here, we aim to review the animal and human data describing the role of dopamine and the mesolimbic dopamine system during acute and chronic alcohol exposure. Finally, preclinical and clinical studies evaluating the potential of available dopaminergic agents as well as indirect dopamine modulators as novel medications for alcohol dependence are discussed.

1.1. The brain reward system: the mesocorticolimbic dopamine system

The mesocorticolimbic dopamine system has an established role in driving the rewarding sensations from natural rewards such as food, sex and exercise, which are important behaviours to ensure our survival [6, 7] as well as among drugs of abuse, including alcohol (for review see [8]). The physiological importance of the mesocorticolimbic dopamine system is highlighted by its evolutionary stability and conservation in primitive invertebrates, such as,

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flatworms, all the way up to primates, including humans. It was identified serendipitously in the 1950s when Olds and Milner found that rats self-administer electrical currents into certain specific brain regions [9]. These findings were later corroborated by studies showing that rats favoured electrical stimulation in the same specific brain regions, over natural rewards [10]. The primary neurotransmitter regulating the rewarding sensation was determined to be dopamine [11]. Furthermore, the specific neuronal circuitries were progressively mapped with major projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc, i.e. the ventral striatum), the prefrontal cortex (PFC) and amygdala. Collectively, this network of neurons was denominated the mesocorticolimbic dopamine system [12, 13]. The system was later divided into two distinct projections [12], modulating different dopamine-mediated behavioural effects; the mesolimbic pathway (from the VTA to the NAc) thought to be responsible for the rewarding and pleasurable effects of natural as well as substances of abuse including alcohol (e.g. [14–16]), and the mesocortical pathway (from the VTA to the PFC) believed to be responsible for the motivational and emotional effects [15]. In addition, there are dopamine projections from the VTA to the amygdala and the hippocampus, respectively, involved in reward associative learning and declarative memory formation [15, 17].

In healthy controls, alcohol consumption stimulates dopamine release mediating its reinforcing effects. Repeated bouts of intoxications will overtime downregulate the dopamine activity in the mesocorticolimbic pathway, leading to an increased risk of developing alcohol dependence and other impulse control disorders. [18, 13]. It has also been hypothesized that in vulnerable individuals (e.g. those with a family history of alcohol dependence), the proneness

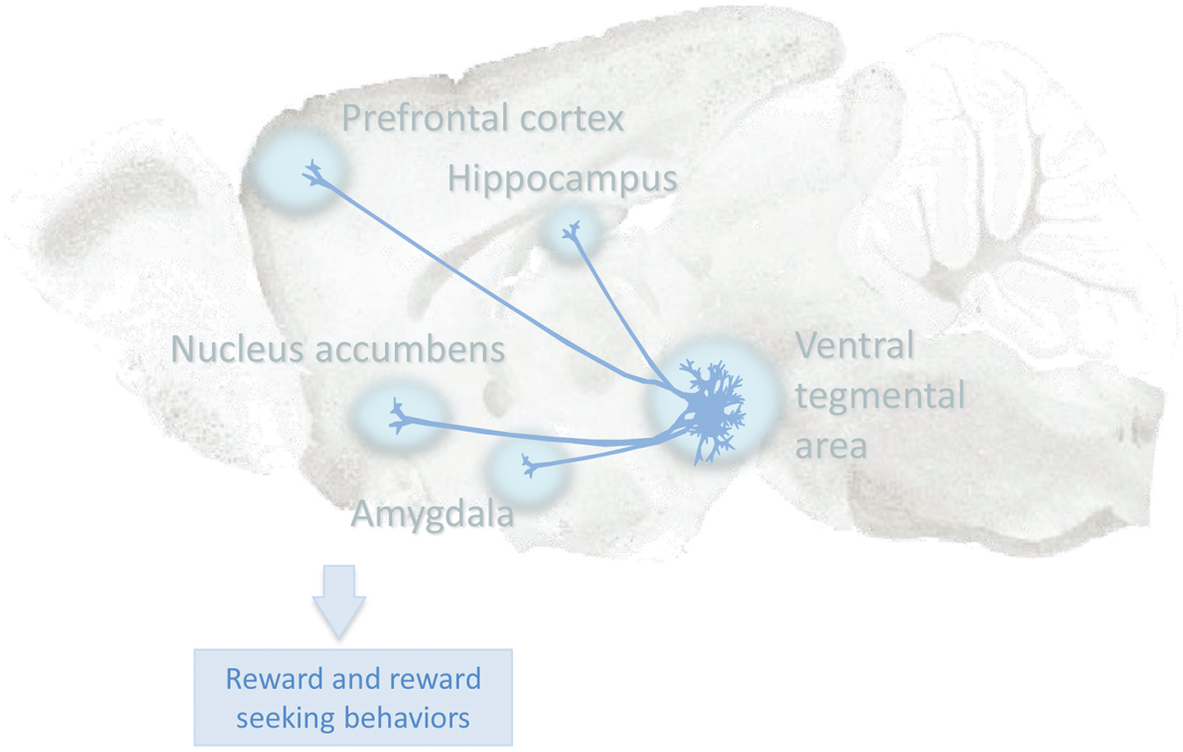

Figure 1. Representative illustration of the mesocorticolimbic dopamine system in rat brain.

to develop an addiction is higher since they are born with a reduced number of dopamine D2 receptors in mesocorticolimbic pathway, leading to the alcohol dependence [18, 13]. Further, it has been speculated that this dopamine deficiency is responsible for driving craving and compulsive drinking and contributes to relapse even after a period of protracted abstinence [18, 19]. The preclinical and clinical evidence of the underlying interaction between alcohol and the dopamine D2 receptors within the mesocorticolimbic dopamine system during the acute as well as during chronic intake is reviewed below. The involvement of the dopamine D1, D3, D4 and D5 receptors falls outside the scope of the present review but has previously been reviewed elsewhere [20].

1.2. Interaction between alcohol and the mesocorticolimbic dopamine system

1.2.1. Preclinical evidence: acute alcohol exposure and dopamine

Dopamine's importance for alcohol-induced reward was first identified in studies showing that the catecholamine-synthesis inhibitor, α-methyltyrosine (an agent with the ability to inhibit the formation of dopamine in the cytosol of terminals of dopaminergic neurons [21]) blocked alcohol-induced euphoria, social interaction and talkativeness in humans [22] as well as attenuated alcohol-induced locomotor activity in rats [23]. *Ex vivo* and *in vivo* voltammetry studies in rats found that alcohol increases the dopamine levels in NAc [24]. In addition, *in vivo* microdialysis studies have since shown that systemic administration of alcohol and other drugs of abuse, including amphetamine, cocaine, opiate and nicotine, increases the accumbal dopamine levels in freely moving rats [25–35], strengthening the hypothesis of an association between the rewarding or euphoric sensation and dopamine release in the NAc. This hypothesis is further supported by studies showing that drugs that are not rewarding or abused by humans do not modify synaptic accumbal dopamine levels in rat [27]. In addition, voluntary alcohol consumption causes a dose-dependent [36] release of dopamine in the NAc in rat [37–39]. Finally, intravenous administration of alcohol, as well as other drugs of abuse, increases the firing rate of dopamine neurons in the VTA in rats [40, 41]. Further support for the role of dopamine D2 receptors in the reinforcing effects of alcohol is given by a study showing that dopamine receptor D2 knockout mice self-administer less alcohol than the wild-type mice [42]. In addition to the extensive literature showing a link between accumbal dopamine and alcohol-induced reinforcement, it has been shown that the pure anticipation of alcohol (i.e. without alcohol being present) increases the release of dopamine in NAc in rodents trained to self-administer alcohol [43–45, 36] and that accumbal dopamine release is associated with associative learning, rather than exposure to the reward itself [46]. Moreover, this anticipation effect is more noticeable in high compared to low-alcohol-preferring rats [47]. Studies have also shown that the anticipation of a reward increases the firing of accumbal dopamine neurons [41]. It should, however, be mentioned that results from studies with lesion of the mesocorticolimbic dopamine pathways have shown contradicting results with both decreased [48–50] and unaltered alcohol intake [51–56]. These inconsistent results indicate that the role of accumbal dopamine in reinforcement is complex and highlights that the rewarding properties of alcohol may extend beyond direct or indirect effects on dopamine, involving interactions

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with several other neurotransmitters including acetylcholine, glutamate, GABA, serotonin (5HT), noradrenaline, taurine and opioids, as well as hormones and peptides [24, 57, 58].

To further elucidate the role of the NAc and the VTA in alcohol-mediated dopamine regulation, extensive rodent studies, with for example intra-cranial alcohol infusions and electrophysiological techniques, have been conducted. With regards to the NAc, rodent studies confirm that intra-NAc alcohol perfusions increase the release of dopamine in the same brain region (e.g. [59, 38, 60–62]). An effect that is suggested to be regulated via a neuronal circuitry involving glycine receptors in the NAc as well as anterior ventral tegmental nAChR [59, 63, 64]. Interestingly, the NAc is a heterogeneous region most often divided into two distinct anatomically and functionally different regions, that is the central core and the surrounding shell compartment [65–69] and it has been suggested that dopaminergic innervation of the NAc core is associated with the nigrostriatal system, while that of the NAc shell is related to the mesolimbic system [70]. Alcohol has been shown to increase the release of dopamine in NAc shell, but not in the core [71–73]. Studies are also emerging suggesting the need for further division of this brain region since it was demonstrated that a borderline region between the core and shell of the NAc is the region most responsive to alcohol [74].

With regards to the VTA, both *in vitro* and *in vivo* studies show that alcohol increases the firing of dopamine neurons in the VTA projecting to NAc [75–79, 40]. Similarly, in a situation of synaptic transmission blockade, alcohol has been found to increase the firing of dissociated VTA dopamine neurons [76, 77] implying that alcohol activates ventral tegmental dopamine neurons independent of afferent signalling. Furthermore, studies with intra-VTA alcohol infusions highlight that different subregions within the heterogeneous VTA might have different ability to modulate the alcohol-induced dopamine response. Specifically, rats voluntarily self-administer alcohol, as well as acetaldehyde (an alcohol metabolite) into the posterior, but not anterior, part of the VTA [80–85], indicating that alcohol is reinforcing only within the posterior VTA. The suggestion is further supported by a study showing that intracranial infusions into the posterior VTA of the D2 agonist quinpirole (in doses that activate local D2 autoreceptors, thereby reducing the firing rate of VTA dopamine neurons [86, 87]), attenuates alcohol self-administration, which can be restored when the D2 agonist is removed or blocked with administration of a D2 antagonist [84]. In corroboration are the findings that the sensitivity of the posterior VTA to the reinforcing effects of alcohol is enhanced in alcohol-preferring rats [88]. There are, however, some contradicting results indicating that these subregion-specific effects might be related to the administered dose of alcohol, the use of various methods, the rat strains across the studies as well as differences in coordinates used for local injections (within the anterior VTA). For example, it has been demonstrated that perfusion of a low, but not a high dose of alcohol into the anterior, but not posterior part of the VTA increased accumbal dopamine in rats [89], and a recent study indicates that additional VTA subregions might be involved as alcohol increases the firing frequency of a subset of dopamine neurons in the medial, but not lateral, part of the VTA [90]. It should also be noted that in both outbreed as well as alcohol-preferring rats, there are studies showing no influence on the accumbal dopamine levels regardless of dose of alcohol or location in the VTA [59, 91]. Collectively, these data suggest that VTA is a heterogeneous area that differs in morphology

and topography (for review, see [92]), and the anterior/posterior and lateral/medial part have different functions regarding alcohol and its activation of the mesolimbic dopamine system.

1.2.2. Clinical evidence: acute alcohol consumption and dopamine

The development of positron imaging technique (PET) and the radiotracer ^{11}C-raclopride in the 1990s made it possible to study *in vivo* dopamine function in humans. A series of human imaging studies over the last decade have demonstrated that alcohol [93, 94] as well as other drugs of abuse [95] increase striatal dopamine release. This is further corroborated by the findings that self-reported behavioural measures of stimulation, euphoria or drug wanting by alcohol correlates with the magnitude and rate of ventral striatum dopamine release [96–98, 94, 99, 100]. These studies clearly substantiated the involvement of dopamine in the reinforcing effects of alcohol and closely mimicked the findings of the preclinical studies.

1.2.3. Preclinical evidence: chronic alcohol exposure and dopamine

As mentioned above, it has been hypothesized that the chronic intake of alcohol induces a dopamine deficit state in the brain reward system and that this dysfunction may drive craving and relapse to drinking [101, 18, 19]. In outbred rodents, however, the effects on the mesolimbic dopamine system following chronic alcohol treatment are inconsistent [102]. One possible explanation for these discrepancies may be that most preclinical studies to-date have used forced alcohol administration which introduces an element of stress and artefact into the experiment, casting doubt on the applicability to our understanding of human alcohol dependence. In this review, we will therefore focus on studies with clear face validity to the human condition, that is those using voluntary self-administration.

The dopamine deficiency hypothesis is supported by a study showing decreased dopamine receptor gene expression after several months of voluntary alcohol drinking [103]. In addition, microdialysis studies in freely moving outbred rats show a decreased dopamine output in the NAc, compared to age-matched alcohol-naïve controls, following 7 weeks [104] and 10 months [29] of voluntary alcohol consumption. Furthermore, after 10 months of drinking, a blunted dopamine response following a systemic alcohol challenge has been found in long-term drinking, compared to alcohol-naïve rats [29]. These results indicate that long-term drinking attenuates the responsiveness of the system to external dopamine stimulation, in addition to decreasing baseline levels of dopamine. It should, however, be noted that acute administration of alcohol induces a twofold increase in dopamine output in the NAc shell in high compared to low-alcohol-preferring rats [105], indicating that there might be a difference in these aspects between outbred standard laboratory rats and inbred alcohol-preferring rats.

The selectively inbred alcohol-preferring and non-alcohol-preferring rat strains have been extensively used to investigate the neurochemical mechanisms underlying alcohol dependence. In line with the dopamine deficiency hypothesis, the baseline accumbal dopamine levels appear to be lower [105] and the dopamine D2 receptors in NAc are fewer [106] in high-preferring compared to low-preferring rats. In fact, neurochemical data show that high-alcohol-seeking behaviour is associated with 10–15% lower accumbal dopamine content

compared with low-alcohol-seeking rats [107]. In addition, overexpression of accumbal dopamine D2 receptors reduces alcohol in non-preferring as well as high-preferring rats [108, 109]. These results highlight that not only chronic alcohol consumption, but also genetic factors, influence the dopaminergic response to alcohol. Furthermore, it has been suggested that more dorsal parts of the striatum is recruited once the dependence develops [110, 111] although until now this has been investigated only in other drugs of abuse than alcohol.

1.2.4. Clinical evidence: alcohol dependence and dopamine

As mentioned earlier, in vulnerable individuals (related to genetic and environmental factors) as well as healthy individuals, repeated administration of alcohol can lead to perturbations in the dopamine-regulated circuitry, leading to the development of alcohol dependence. For instance, a human laboratory study has demonstrated that intravenous administration of alcohol causes an increase in dopamine in the ventral striatum in non-treatment-seeking alcohol-dependent individuals [112]. Further, imaging studies have shown that the number of dopamine D2 receptors is lower in individuals with alcohol or drug dependence, compared to healthy controls [113, 114] and there is considerable evidence that the low levels of D2 receptors levels contribute to the excessive urges/craving for alcohol and subsequently to relapse [115]. In addition, decreased dopamine transmission in the mesolimbic regions, such as the ventral striatum, likely contributes to anhedonia and decreased reward sensitivity in alcohol-dependent individuals. Further, in abstinent high-risk drinkers as well as alcohol-dependent individuals, alcohol-associated cues activate the ventral striatum, which further contribute to the high risk of relapse in these individuals [116, 117].

A recent PET study [118] demonstrated for the first time that, in addition to the ventral striatum, the long-term consumption of alcohol leads to lowered dopamine levels also in prefrontal cortical structures. These findings support the extensive clinical findings demonstrating that alcohol-dependent individuals have significant impairments in executive functions such as working memory, impulsivity and decision-making; functions governed by the cortical brain structures. The fact that there is also less dopamine in the prefrontal cortex, governing these executive functions, is of significance as it could impair the alcohol-dependent individual's capacity to utilize behavioural treatment strategies, which are critical to relapse prevention.

Collectively, these data indicate that dopamine plays a central role in reward, motivation and planning. Given the relevance of dopamine in the chronic phase of alcohol use and in the development of alcohol dependence, there is considerable interest in evaluating medications that can specifically modify dopamine, thereby serving as potential pharmacotherapies to treat alcohol dependence.

1.2.5. Human genetic evidence: alcohol dependence and dopamine

The preclinical and clinical evidence presented above suggest that dopamine regulates alcohol-mediated behaviours. Numerous human genetic studies have therefore investigated associations between alcohol dependence and genes related to dopamine function. As early as the

1990s, a polymorphism in the dopamine D2 receptor gene was found to be associated with alcohol dependence [119]. Several studies have since then tried to replicate this association, but the outcome has been inconsistent (for review, see [120]). Although associations have been found between polymorphism of the dopamine D4 gene and alcohol craving, binge drinking as well as novelty seeking (which is a known personality trait important for drinking behaviour in patients with alcohol dependence) [121–123], no positive associations between dopamine D4 receptor genes and alcohol dependence *per se* have been established (for review, see [120]).

Released dopamine into the synaptic cleft is eliminated by catechol-O-methyltransferase (COMT) metabolism as well as reuptake by dopamine transporter (DAT). Studies have shown that DAT polymorphism is associated with alcohol withdrawal symptoms as well as with paternal history of alcohol dependence rather than alcohol dependence *per se* [124, 125]. The risk of developing late onset alcohol dependence (especially in males) as well as the co-dependence of alcohol and nicotine is associated with polymorphism in COMT [126–128]. Albeit cumulative evidence shows association between polymorphisms in various dopamine-related genes and behaviours associated with alcohol dependence, the findings are inconclusive and therefore, the conclusions from these human genetic studies are limited and remain controversial.

2. The dopamine system: a potential treatment target for alcohol dependence

2.1. Dopamine D2 receptor antagonists

Traditional dopamine D2 receptor antagonists (so-called neuroleptics, first-generation antipsychotic drugs or typical antipsychotic drugs) are primary used for the treatment of psychosis, schizophrenia and bipolar disorder [11] based on their ability to counteract a heightened dopamine activity in the brain. It should also be mentioned that these typical antipsychotic agents might have effects on other receptors including dopamine D1, $5HT_2$ and alpha1 receptors. As reviewed above, the acute reinforcing effects of addictive drugs, including alcohol, could be mediated by increased dopamine release in the NAc, activating dopamine D2 receptors [71, 27, 30]. Thus, traditional dopamine D2 receptor antagonists have been evaluated as potential treatment targets for alcohol dependence based on the hypothesis that they are expected to block the rewarding effects of alcohol.

2.1.1. Preclinical evidence for the use of dopamine D2 receptor antagonists to attenuate alcohol-mediated behaviours

The hypothesis that dopamine D2 receptor antagonists have the ability to attenuate alcohol-mediated behaviours is supported by rodent studies showing that both haloperidol and pimozide attenuate alcohol-induced locomotor stimulation [129] and that these compounds as well as fluphenazine, decrease alcohol-seeking behaviour and operant self-administration [130–132]. These findings are further substantiated by the data showing that peripheral

administration of the dopamine D2 receptor antagonist fluphenazine decreased responding for alcohol, without affecting responses for water in rats [133]. In addition, haloperiodol dose-dependently reduced operant self-administration of alcohol in rats [134] as well as decreased alcohol presentations in the self-administration model [132]. Supportively, low doses of dopamine D2 receptor antagonists inhibit the rewarding properties of other drugs of abuse in rats [135, 42, 136]. It should be noted that some studies have shown contradicting effects [137–139], indicating that the role of dopamine in alcohol-mediated behaviours in complex.

Studies elucidating the underlying mechanism of action of the complex dopamine–alcohol interaction have been conducted. Experiments exploring the role of accumbal dopamine receptors in alcohol-mediated behaviours showed that intra-NAc administration of first-generation antipsychotic drugs including fluphenazine or raclopride decreased alcohol self-administration in rats [133] as well as the total responding for alcohol [140] and reduced the total responding by decreasing time course and response rate for alcohol self-administration in rats [141]. On the other hand, local administration of the dopamine D2 receptor antagonist, sulpiride, into the anterior VTA did not alter alcohol nor sucrose intake in high-alcohol-preferring rats [142]. It should also be mentioned that accumbal dopamine D1 receptor might regulate alcohol-induced reward. Indeed, intra-NAc infusion of a dopamine D1 receptor antagonist (SCH23390 or ecopipam) decreased alcohol-mediated behaviours in rats [141, 143]. Collectively, these data indicate that the dopamine D2 as well as D1 receptors within the NAc regulate alcohol reinforcement.

2.1.2. Clinical evidence for the use of dopamine D2 antagonists for the treatment of alcohol dependence

Based on the preclinical evidence of a reduction in alcohol consumption via blockade of dopamine D2 receptors, the potential of dopamine D2 antagonists as a pharmacotherapy for alcohol dependence has been investigated in clinical populations.

Dopamine D2 receptor antagonists have been studied in human laboratory studies involving alcohol administration in dependent individuals and found to be effective in reducing craving. In a laboratory study involving 16 individuals with alcohol abuse and/or dependence, the D2 antagonist haloperidol was compared to placebo. The results of this small study demonstrated that haloperidol significantly decreased measures of craving, reduced impulsivity, and the amounts of alcohol ingested [144]. The dopamine D2 antagonist flupenthixol has also been evaluated in a clinical study of 281 recently detoxified alcohol-dependent patients [145]. The results demonstrated that treatment with the depot formulation of flupenthixol led to a significant increase in rates of relapse (85.2% on active treatment compared with 62.5% on placebo). A major concern with flupenthixol is results from studies demonstrating an increase in the risk of relapse in rodents as well as humans [146], an effect preferentially observed in males [147]. Overall, the clinical utility of atypical antipsychotics has shown to be of some benefit in patients suffering from alcohol dependence and a concomitant psychiatric diagnosis including schizophrenia [148, 149]. A major challenge, however, with the first-generation antipsychotic drugs is their severe side effect profile including extrapyramidal symptoms, sedation, cognitive impairment, neuroleptic malignant syndrome, which have limited their use in research and in turn its clinical utility in treating alcohol dependence [150, 151].

2.2. Atypical dopamine D2 receptor antagonists

The newer generations of dopamine D2 receptor antagonists (so-called atypical antipsychotics or second generation antipsychotic drugs) have a broader pharmacological profile since they target several dopamine receptors, including D1, D3, D4 and D5, as well as various other neurotransmitter systems including 5-HT, muscarinic acetylcholine and histamine receptors. These atypical antipsychotics have a significantly improved side effect profile compared to the traditional first generation of dopamine D2 antagonists. Thus, there has been a renewed interest in evaluating these medications as potential treatment for alcohol dependence with the assumption that the atypical antipsychotics might reduce craving and consumption of alcohol without the substantial adverse effect profile [152]. Furthermore, they are clinically used for alcohol-dependent patients during the acute detoxification phase to prevent agitation, hallucinations and delirium tremens [153].

2.2.1. Preclinical evidence for the use of atypical dopamine D2 receptor antagonists (i.e. atypical antipsychotics) to attenuate alcohol-mediated behaviours

The hypothesis that atypical antipsychotics may decrease alcohol intake are supported by two separate studies with risperidone and olanzapine in high-alcohol-preferring rats [154, 155]. Furthermore, remoxipride decreases the number of alcohol presentations per session in rats by inducing an early termination of the alcohol-drinking bout during the self-administration session [132] and repeated systemic administration of paliperidone decreased the acquisition of alcohol consumption in high-alcohol-preferring P rats [156]. In addition, a recent study, comparing the effect of the atypical antipsychotic drug clozapine to that of the traditional dopamine D2 receptor antagonist haloperidol, showed that clozapine but not haloperidol attenuated the initiation of alcohol drinking and development of alcohol preference in high-alcohol-preferring rats [157]. Neither compound had an effect on maintenance of chronic alcohol drinking [157], which is in line with a study showing that clozapine did not reduce alcohol consumption in alcohol-preferring rats [155].

2.2.2. Clinical evidence for the use of atypical dopamine D2 antagonists for the treatment of alcohol dependence

The atypical antipsychotic tiapride has been found to be efficacious in reducing alcohol drinking two placebo-controlled clinical trials [158, 159]. A small study in twenty alcohol-dependent individuals, with significant levels of anxiety or depression, showed that tiapride treatment causes a reduced alcohol intake as well as prolonged periods of abstinence [158]. In the largest of the studies [159], 100 recently abstinent alcohol-dependent patients were randomized to 300 mg of tiapride or placebo for a 3-month treatment period. This study showed that patients receiving medication had higher rates of abstinence and improved on an array of health care outcomes.

Another atypical antipsychotic drug, quetiapine, has been evaluated in a case study [160] and an open-label study [161] in patients with alcohol dependence and comorbid psychiatric diagnosis. Both studies demonstrated that quetiapine was well tolerated and in the latter study, the medication not only reduced alcohol consumption and overall psychiatric symptom

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intensity but also significantly reduced craving. A double-blind placebo-controlled study by Kampman and colleagues evaluated the effect of quetiapine and found that the medication was well tolerated and clinically effective in reducing drinking [162]. The effect of medication was found to be stronger in individuals with a more severe disease phenotype. It should, however, be noted that more recent clinical trials using the extended release formulation of quetiapine [163, 164] failed to replicate the clinical findings of the previous studies.

In a retrospective study of 151 schizophrenic patients with alcohol dependence, 36 patients received the atypical antipsychotic medication clozapine. At the 6-month follow-up, 79% of the patients on clozapine were in remission from a diagnosis of alcohol dependence, while approximately 33% of those not taking clozapine were in remission [148].

Olanzapine, another example of a second generation of antipsychotics, has been evaluated in a human cue-craving study, where the compound reduced the urge to drink post-exposure to alcohol cues, without affecting the rewarding effects of alcohol following the consumption of a priming dose of alcohol [152]. Based on this clinical finding and the knowledge that olanzapine also has a high affinity for the D4 receptors, it was hypothesized whether the dopamine receptor D4 gene maybe involved in meditating its clinical effects. In a subsequent pharmacogenetic, 12-weeks placebo-controlled trial in heavy social drinker olanzapine was evaluated in 67 individuals [165] showing that those individuals with the dopamine D4 receptor 7 repeat allele (a polymorphism of the dopamine D4 receptor gene) reported a greater reduction in cue-induced craving and alcohol consumption compared to individuals with the short allele. These data are supported by the findings that olanzapine reduces craving for alcohol at baseline for both individuals with the DRD4 shorter and longer allele, but only reduces craving after exposure to alcohol cues and after a priming dose of alcohol for individuals with the DRD4 longer allele [166]. Overall, the results from studies evaluating olanzapine as a potential medication for alcohol dependence have provided evidence of a marginal effect restricted to a sub population of patients (with the longer dopamine D4 receptor allele).

In conclusion, although some clinical trials with atypical antipsychotics in alcohol-dependent patients show promising results, a recent systemic review of atypical antipsychotics, a heterogeneous class of drugs [167] has demonstrated inconsistent clinical response across studies on these compounds effects on alcohol-related parameters. The clinical use of atypical antipyschotics for treatment of alcohol dependence might also be limited by their side effects profile, even though it is substantially improved compared to the typical antipsychotics (for review see [168]).

2.3. Dopamine D2 agonists

As described previously, in vivo microdialysis studies rodent and imaging studies in individuals with alcohol dependence have demonstrated that chronic exposure to alcohol induce a dopamine deficit state. Thus, it is logical to hypothesize that a dopamine agonist would substitute for this dopaminergic dysfunction during alcohol dependence and alleviate the associated depression-like symptoms and craving for alcohol.

2.3.1. Preclinical evidence for the use of dopamine agonists to attenuate alcohol-mediated behaviours

The potential of dopamine D2 agonists to regulate alcohol-mediated behaviours is supported by a study showing that apomorphine, dose-dependently reduces operant self-administration as well as decreases momentary response rates for alcohol in rats [134] and that SDZ-205-152, a synthetic-mixed D1/D2 dopamine receptor agonist dose-dependently reduces self-administration of alcohol, but not water, in rats [169]. Moreover, cabergoline, a dopamine D2 receptor agonist, decreased alcohol intake, relapse drinking as well as alcohol-seeking behaviour in rodents [170]. In addition, low doses of bromocriptine produced a significant, dose-dependent shift in decreasing the preference for alcohol while enhancing water consumption [171], indicating that the compound at lower doses preferentially augment autoreceptor function, leading to decreased dopamine turnover with a blunted response to the rewarding effects of alcohol as a result. Studies with intra-NAc administration of quinpirole, further indicating that D2 receptors are involved in a biphasic effect on alcohol self-administration, by showing that low doses of the agonist increase, whereas higher doses decrease, self-administration of alcohol [141] (but see also [140]). A study has also investigated the effect of dopamine D2 receptor agonist administration into VTA on alcohol intake. This study showed that microinjection of either quinpirole or quinelorane, into the anterior part of the VTA dose-dependently decreased alcohol, but not sucrose, intake in alcohol-preferring rats [142]. In support are the data showing that local administration of cabergoline into the VTA reduced alcohol-seeking behaviour in rats [170]. These data are contradictory to the findings showing that the dopamine D2 receptor antagonist into the anterior VTA did not alter alcohol intake in high-alcohol-preferring rats [142]. Therefore, mechanisms regulating alcohol reinforcement might be different in selectively breed high alcohol-consuming rats compared to outbreed rats, and this should be investigated in more detail. It should also be mentioned that infusion of the dopamine D1-like agonist SKF 38393 into NAc had no effect on alcohol self-administration in rats [141]. Albeit the data are somewhat contradictory, it might be hypothesized that accumbal as well as ventral tegmental dopamine D2 receptors may regulate alcohol reinforcement in rodents.

2.3.2. Clinical evidence for the use of dopamine agonists for the treatment of alcohol dependence

Bromocriptine, a dopamine agonist has been used clinically for Parkinson's disease. At low doses, bromocriptine can reduce alcohol consumption in animals [171]; it is possible that low-dose dopamine agonists preferentially augment autoreceptor function, thereby decreasing dopamine turnover and blunting the rewarding effects of alcohol. An early double-blinded study [172] reported that bromocriptine reduced alcohol craving in alcohol-dependent patients with a specific genotype of the dopamine D2 receptor gene (i.e. the A1/A1 and A1/A2 genotypes). However, subsequent double-blind placebo-controlled trials found no effect on relapse or related behaviours [173, 174]. Currently, due to the knowledge of the addictive potential of dopamine agonists, combined with the lack of consistent findings from clinical studies, it is suggested that dopamine receptor agonists do not hold promise as a treatment for alcohol dependence.

2.4. Partial dopamine agonists

Based on the knowledge that alcohol can both stimulate dopamine activity as well as induce a hypo-dopaminergic state, it has been suggested that partial agonists might have potential as novel medications for alcohol dependence. A partial agonist, such as aripiprazole, has a lower intrinsic activity at the receptor than a full agonist (e.g. dopamine), meaning that when it binds to the receptor, it will activate the receptor but produce a less potent biological response than the full agonist [175–177]. In the presence of high levels of the full agonist, a partial agonist will have functional antagonistic activity by binding to the receptor and preventing the response from the full agonist. Partial dopamine D2 agonists, therefore, offer the opportunity to treat the dysregulated dopamine activity during acute alcohol consumption as well as alcohol dependence.

2.4.1. Preclinical evidence for the use of partial dopamine agonists to attenuate alcohol-mediated behaviours

In line with the hypothesis that a partial dopamine D2 agonist would block the reinforcing effects of alcohol, aripiprazole attenuates alcohol's ability to increase the locomotor activity in mice [178, 179](an indirect measure of activation of the mesolimbic dopamine system). On the other hand, aripiprazole did not interfere with the alcohol-induced impairment in motor balance as measured by rotarod test [179]. Furthermore, repeated systemic aripiprazole administration decreases alcohol intake in alcohol-preferring rats [180], while single oral administration dose-dependently decreases alcohol self-administration in outbred rats [181]. In addition, aripiprazole has been shown to reverse alcohol-induced place preference and anxiety-like behaviour in mice [182].

2.4.2. Clinical evidence for the use of dopamine partial agonists for the treatment of alcohol dependence

Clinically, the partial dopamine D2 agonist aripiprazole has been evaluated in a few randomized placebo-controlled trials and human laboratory studies. A pilot study showed that aripiprazole reduces the rate of relapse and craving in patients with alcohol dependence [183]. In a subsequent larger 12-weeks, double-blind, placebo-controlled study of 295 alcohol-dependent patients aripiprazole was initiated at 2 mg/day, titrated to a maximum dose of 20 mg/day [184]. This study showed that aripiprazole decreased heavy drinking days compared to placebo during week four and eight; however, the effect was lost by the maximum dose at week twelve [184]. The effects of aripiprazole were also evaluated in a human laboratory study in non-treatment seeking alcohol-dependent individuals (n = 30), showing that the compound was well-tolerated and reduced drinking, especially in impulsive individuals [185]. Voronin and colleagues also showed that aripiprazole decreased the number of drinks in a bar–lab environment after consumption of a priming drink, as well as weakened the association between the priming-induced stimulation and further drinking. In another double-blind comparison trial, aripiprazole was shown to reduce craving [186] but to a lesser extent than the FDA-approved medication naltrexone [187]. Finally, a brain imaging study demonstrated that aripiprazole attenuated cue-induced activation as evidenced by a reduced activation of the right ventral striatum with a corresponding reduction in drinking in individuals with

alcohol dependence [188]. Thus far, early results with aripiprazole appear promising, although whether this or similar compounds might be useful to treat alcohol dependence or be positioned as a medication with a specific profile, that is as targeted intervention in more impulsive alcohol-dependent individuals needs to be evaluated further.

2.5. Dopamine stabilizers

As a further development of the partial agonist concept, Nobel Laureate Arvid Carlsson and co-workers, developed a novel family of compounds based on their ability to stabilize, that is to stimulate, suppress or show no effect on the dopamine activity depending on the prevailing dopaminergic tone [189]. This stabilizing concept was postulated based on a PET study in rhesus monkeys where infusions with the compound (-)-OSU6162 (OSU6162) induced a dopaminergic tone-dependent effect with a reduction in the striatal L-[11C]DOPA influx rate in monkeys with high baseline values and an increased striatal L-[11C]DOPA influx rate in animals with low baseline values [190]. The mechanism of action is, however, not completely understood, and although *in vitro* studies indicate that OSU6162, like aripiprazole, acts as a partial agonist at D2 receptors [191, 192], behavioural studies have failed to demonstrate any intrinsic activity of the compound ([195]). Instead it has been suggested that OSU6162 produces functionally opposite effects by acting as an antagonist at both presynaptic autoreceptors and postsynaptic D2 receptors [189, 193–195]. Based on the hypothesis that OSU6162 can counteract both hyper- and hypo-dopaminergic states, the compound has recently been evaluated in both animal models modulating alcohol-mediated behaviours as well as in a placebo-controlled human laboratory study in alcohol-dependent patients.

2.5.1. Preclinical evidence for the use of dopamine stabilizers to attenuate alcohol-mediated behaviours

A series of experiments in outbred rats show that the dopamine stabilizer OSU6162 attenuates several alcohol-mediated behaviours including voluntary alcohol intake, alcohol withdrawal symptoms and cue/priming-induced reinstatement of alcohol seeking in long-term drinking rats [196]. Furthermore, OSU6162 blunted alcohol-induced dopamine output in the NAc of alcohol-naïve rats [196], indicating that OSU6162 has the ability to attenuate the rewarding effects of alcohol. In contrast, a more recent microdialysis study conducted in long-term drinking rats, showed that OSU6162, compared to vehicle-pretreatment, had no significant effect on the alcohol-induced dopamine peak [29]. The contrasting microdialysis results in alcohol-drinking versus alcohol-naïve rats highlight OSU6162´s ability to modulate the dopamine output dependent on the prevailing dopaminergic tone. Furthermore, these results indicate that OSU6162 might have the ability to attenuate alcohol-mediated behaviours by counteracting the hypo-dopaminergic state induced by long-term drinking. Collectively, together with the finding that OSU6162 did not induce conditioned place preference [29] (an indication that the compound has no rewarding properties of its own), these results indicate that OSU6162 has many of the favourable characteristics of a potential medication for alcohol dependence.

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2.5.2. Clinical evidence for the use of a dopamine stabilizer for the treatment of alcohol dependence

The dopamine stabilizer OSU6162 was recently evaluated in a placebo-controlled human laboratory alcohol craving study in 56 alcohol dependent individuals [197]. Two weeks of OSU6162 treatment significantly attenuated priming-induced craving and induced significantly lower subjective "liking" of the consumed alcohol, compared to placebo. Interestingly, the treatment effects of OSU6162 were driven by those individuals with high level of baseline impulsivity, corroborating previous results with the partial dopamine D2 agonist aripiprazole [185]. These results suggest that pharmacological stabilization of the dopamine system might prove as an effective target for alleviating some of the reward driven behaviours during alcohol dependence. Together with OSU6162's favourable side effect profile [198, 197, 199], these results render support for a larger placebo-controlled efficacy trial in alcohol-dependent patients to evaluate OSU6162's effect on drinking outcomes.

2.6. Pharmacological agents inducing indirect modulation of dopamine

As mentioned previously, in addition the affecting the dopamine system directly, alcohol interacts with the mesolimbic dopamine system indirectly via several other neurotransmitters. There is a wide range of such compounds, and here, we will only mention a few, specifically targeting glycine receptors and nAChRs, with a clear interaction with dopamine transmission in the mesolimbic dopamine system [64].

2.6.1. Preclinical evidence for the use of compounds that indirectly targets dopamine to attenuate alcohol-mediated behaviours

Rodent studies exploring the potential of targeting the glycine system as a medication for alcohol dependence showed that systemic administration of the glycine transporter-1 inhibitor Org25935 increased extracellular glycine in the NAc, which prevented alcohol-induced dopamine release [200, 201] as well as decreased alcohol intake and prevented relapse drinking [202, 203]. These results provided rational for a randomized placebo-controlled clinical trial in alcohol-dependent individuals.

Emerging data suggests that the activity of dopamine neurons in the VTA projecting to the NAc is regulated by several afferents, such as, for example the cholinergic neurons projecting from the laterodorsal tegmental nucleus (LDTg) (for review see [204]). Although alcohol's direct interaction with this cholinergic-dopaminergic reward link remains to be fully elucidated, a study show that voluntary alcohol intake in high-alcohol-consuming rats causes a concomitant release of ventral tegmental acetylcholine and accumbal dopamine [39]. Several rodent studies with nAChR antagonists such as mecamylamine or selective nAChRs antagonists such as alpha-conotoxin MII highlight the potential of nAChRs as novel medications for alcohol dependence by showing that these compounds prevent alcohol from increasing dopamine and reduce alcohol consumption behaviour [28, 38, 32, 34, 35]. These nAChR antagonists are limited in a clinical setting due to low blood–brain barrier permeability and an unfavourable side effect profile. The potential of nAChR's as novel treatment target was revived with the marketing of the partial nAChR agonist varenicline as a smoking cessation

agent. It has been shown that varenicline reduce alcohol intake and alcohol-seeking behaviour in long-term drinking rats [205] and modulate NAc dopamine after systemic administrations of alcohol alone and in combination with nicotine [206].

2.6.2. Clinical evidence for the use of indirect modulation of dopamine for the treatment of alcohol dependence

Albeit the preclinical data look promising regarding the glycine transporter-1 inhibitor Org25935, the multicenter randomized clinical trial produced a negative outcome on alcohol intake, but did not discard the potential importance of the mechanism [207]. More promising clinical studies with varenicline show that this agent decreased alcohol consumption and craving in an experimental setting in heavy-drinking smokers [208–210]. Moreover, data from a randomized clinical trial in alcohol-dependent individuals show that the smoking cessation agent reduced the weekly percent heavy drinking days drinks, decreased the drinks per drinking day as well as prevented alcohol craving [211]. It should, however, be noted that recent clinical trials in alcohol-dependent individuals were unable to find a beneficial effect of varenicline based on self-reported alcohol consumption [212, 213]. Nevertheless, when also monitoring the selective alcohol biomarker phosphatidylethanol (PEth) in the blood of the subjects in the above-mentioned clinical trial [212], it was found that varenicline indeed had effect on this objective measure of alcohol consumption [214] strengthening the potential of varenicline as potential novel medication for alcohol dependence. Besides glycine receptors and nAChR, there are various signalling systems indirectly targeting the mesolimbic dopamine system with promising preclinical findings on alcohol-mediated behaviours. Collectively, these data indicate that indirect modulation of dopamine signalling might be a potential target for novel treatment strategies for alcohol dependence and that these targets should be investigated in more detail in human laboratory studies as well as randomized clinical trials.

3. Conclusion

Extensive preclinical and clinical research support the hypothesis that alcohol's acute reinforcing effects are mediated through a dopamine surge in the mesocorticolimbic dopamine system and that the chronic and excessive alcohol consumption, in contrast, induces a dopamine deficient state driving the processes of craving and relapse. In addition, it is well substantiated that alcohol affects dopamine directly via the NAc and VTA as well as through indirect activation of the mesolimbic pathway via interaction with other reward-related brain regions and neurotransmitters. These complex relationships need to be investigated further. Given dopamine's pivotal role in the development and maintenance of alcohol dependence, medications targeting dopamine does constitute an important area of research. Although promising preclinical results, the majority of results from the clinical studies with dopamine-acting medications have thus far been discouraging. The side effects profile of many of the evaluated compounds, including typical antipsychotic drugs, render them clinically unfav-

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ourable. On the other hand, newer dopamine agents, without complete antagonism or agonism, especially the dopamine stabilizers show promise and deserve further investigation in alcohol-dependent patients.

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