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•Review•

The dopamine system and alcohol dependence

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Summary: Alcohol dependence is a common mental disorder that is associated with substantial disease burden. Current efforts at prevention and treatment of alcohol dependence are of very limited effectiveness. A better understanding of the biological mechanisms underlying dependence is essential to improving the outcomes of treatment and prevention initiatives. To date, most of the efforts have focused on the key role of the dopamine system in the complex etiological network of alcohol dependence. This review summarizes current research about the relationships between alcohol consumption and the dopaminergic system. We find that many of the currently available studies have contradictory results, presumably due to differences in methodology, non-linear dosage effects, use of different samples, and the possible confounding effects of other neurotransmitter systems.

Keywords: dopamine, alcohol dependence, neurobiochemistry, review

1. Introduction

Alcohol is one of the most widely used psychoactive substances in the world. Alcohol-induced changes in brain functions can lead to disordered cognitive functioning, disrupted emotions and behavioral changes. Moreover, these brain changes are important contributing factors to the development of alcohol use disorders, including acute intoxication, long-term misuse and dependence. According to a survey sponsored by the World Health Organization, approximately 50% of the world adult population drank alcohol in 2004 and 76 million individuals met criteria for alcohol-related mental or behavioral disorders listed in the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[1] A report on the relative contribution of different conditions to the 'global burden of disease' (which considers both premature mortality and disability) found that in 2010 alcohol ranked third out of the 25 major causes of the global burden of disease. In high-income countries the relative importance of alcohol-related health problems compared to other health problems is usually greater than in low- and middle-income countries.[2] Alcohol dependence, one of the most important alcohol-related conditions, is widely recognized as a growing global problem with serious medical, economic and social consequences.

Ethanol is a liposoluble neurotropic substance which penetrates the blood-brain barrier and inhibits central nervous system (CNS) functions; it is directly toxic to the brain. The etiology and pathology of alcohol dependence is the outcome of a complex interplay of biological, psychological and socio-environmental factors. CNS neurotransmitters play an important role in the development of alcohol addiction. Previous studies identified a wide range of neurotransmitters related to alcohol metabolism including dopamine, 5-HT, γ-aminobutyric acid, glutamate, endogenous opioid transmitter, acetylcholine and norepinephrine.[3] This review summarizes research progress in understanding the relationships linking the dopaminergic system and alcohol consumption.

2. The dopamine system and brain reward circuitry

The dopamine (DA) system in the CNS includes the nigrostriatal pathway, the mesolimbic pathway and the tuberoinfundibular pathway. Dopamine is mainly

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produced in the substantia nigra, projected along the nigrostriatal pathways and stored in the striatum. Five subtypes of DA receptors have been identified and cloned. All of them function both individually and interactively as G-protein coupled receptors.

There has been continuous research since the 1970s on the role DA plays in the brain reward system. The reward reinforcement circuitry is part of the limbic system that includes the ventral tegmental area (VTA), nucleus accumbens (NAc), ventral striatum, bed nucleus of the stria terminalis, hippocampus, amygdale, and other brain structures. DA is the main neurotransmitter of this system.[4-8] The reward system modulates primary physiological functions related to survival including the intake of food and water and sexual behavior. It is also the target of psychoactive substances including alcohol, cocaine, amphetamine and opioids. The mesolimbic DA pathway (the NAc is the central regulation structure for the reward effect) and the mesocortical pathway are the key structures that modulate the reward reinforcement circuitry.[4-8]

3. Influence of alcohol consumption on the dopaminergic system

Several studies have confirmed a dose-response relationship between alcohol intake and DA release in the NAc.[9-11] Other experiments have also found that injection of ethanol in the NAc induces local DA release in a dose-response fashion.[11-12] In 2000 Yoshimoto and colleagues[13] reported a dose-related elevation of extracellular DA levels in the amygdala after intraperitoneal injection of ethanol and a delayed elevation of DA after ethanol injection in the central amygdaloid nucleus via a microdialysis membrane.[13] These results suggest that the amygdala, part of the reward circuitry, plays a central role in the alcohol-induced effects on the brain. Yim and colleagues[14] documented the process of DA release in the brain induced by various doses of ethanol (0-2.0 g/kg). They found that extracellular DA levels did *not* respond to ethanol in a linear fashion with high doses (1 and 2 g/kg); the DA level returned to baseline within 90 minutes while the ethanol level was still elevated.[14] This suggests acute tolerance to ethanol-induced DA release in the NAc and that ethanol-induced DA release is dependent on the concentration of ethanol. Research by Yim and Gonzales[10] exploring the underlying mechanism of ethanol-induced DA release using animal models found that ethanol increases DA via the promotion of synaptic terminal DA release rather than via the inhibition of DA transporters.[10] Other studies found that ethanol can also indirectly increase DA levels by affecting GABAergic neurons and opioid receptors in the NAc.[15-17]

Other lines of research related to alcohol withdrawal reinforce this model of alcohol-related changes in DA. Electrophysiological studies found that acute ethanol intake can increase DA neuron discharge in the nigra and VTA; this discharge is reduced during alcohol withdrawal and restored after restarting ethanol intake.[18] Animal studies also found that alcohol withdrawal is related to reduced release of DA in the striatal.[19] This suggests that the negative mood during alcohol withdrawal is related to the inhibition of DA in the limbic system and that the voluntary alcohol intake of animals experiencing withdrawal may be reinforced by restoration of DA levels in relevant brain areas after re-initiation of alcohol intake.

Researchers have successfully bred several lines of rats to aid in research about alcohol use and alcohol dependence[4,20]: (a) alcohol-preferring (P) / alcohol-nonpreferring (NP) rats; (b) high-alcohol-drinking (HAD) / low-alcohol-drinking (LAD) rats; (c) University of Chile bibulous (UChB) /University of Chile abstainer (UChA) rats, (d) Alko alcohol (AA) / Alko non-alcohol (ANA) rats, (e) Sardinian alcohol-preferring (sP) / Sardinian alcohol–nonpreferring (sNP) rats, (f) high alcohol consuming (HARF) / low alcohol consuming (LARF) rats and so forth. Alcohol-preferring rats are of special importance for research on the role of DA in alcohol preference because rats highly susceptible to alcohol dependence have defects of the DA system in the mesolimbic pathways.[4,20-22] Using these rat models, researchers have located lower extracellular baseline DA levels in the cerebral cortex and NAc in P rats;[21,22] in the striatal, olfactory tubercle and NAc in HAD rats;[22,23] and in the NAc in UChB rats.[24] Smith and Weiss[25] injected ethanol intraperitoneally to P rats, NP rats and genetically heterogeneous Wistar rats for five consecutive days and found elevated extracellular DA levels in P rats and Wistar rats but not in NP rats. Bustamante and colleagues[20] found that intraperitoneal injection of saline water to UChB and UChA did not induce any changes in the extracellular DA levels in the NAc, but injection of ethanol induced significant increase in DA levels in both lines of rats. Furthermore, ethanol affects the release of DA in the CNS more in UChB rats than UChA rats. Tuomainen and colleagues found[26] that microdialysis of ethanol (of varying concentrations) in the NAc area induced dose-related increases in extracellular levels of DA among AA and ANA rats, and the inceases in AA rats were more than those in ANA rats. Katner and Weiss[27] studied HAD/LAD, AA/ANA, and Wistar rats, and found elevated extracellular basal DA levels induced by intraperitoneal injection of ethanol; moreover, the degree of elevation of DA levels predicted subsequent alcohol drinking behavior. In summary, these studies suggest that ethanol-induced increases in extracellular DA in the CNS NAc and amygdala play a role in ethanol preference.

Not all studies support this conclusion. Some experiments found no difference in DA release in the NAc after intraperitoneal injection of ethanol between P and NP rats. For example, Yoshimoto and colleagues[11] and Gongwer and colleagues[23] found that although HAD and LAD rats differed in their basal level of extracellular DA, they did not differ in CNS DA release after intraperitoneal injection of ethanol. Similarly, Kiianmaa and colleagues[28] found no differential increase of extracellular DA concentration in the NAc between AA and ANA rats after microdialysis of ethanol.

These varying results may be due to the use of different animal models or different research protocols.

Methylphenidate (MP) is a stimulant that inhibits the DA transporter and increases the level of extracellular DA;[29] some researchers suggest that this is associated with the subjective feeling of being 'high'.[30] Positron emission tomography (PET) using radiolabelled raclopride (^{11}C-RAC)—a D2 antagonist that competes with endogenous DA – can be used to observe changes in extracellular DA levels. Using this method, MP was found to decrease the binding of ^{11}C-RAC to receptors in a dose-responsive fashion which indirectly suggested an increased binding of DA to receptors; moreover, the magnitude of DA release was positively correlated with the intensity of MP-induced subjective feeling of being 'high'.[30] Recently, Setiawan and colleagues have found decreased binding of ^{11}C-RAC to DA receptors (which suggest increased extracellular DA levels) among youths at high risk for alcohol dependence.[31] This finding in humans parallels the animal studies by Katner and Weiss;[27] both sets of studies provide support for a quantitative dose-response relationship between DA functioning and the intensity of the reward effect after the intake of psychoactive substances (including alcohol).

In addition to the effect of ethanol on DA release, it can also affect the functioning of DA receptors, particularly D2 and D1 receptors. The D1 receptor binds with excitatory G protein and activates adenylate cyclase (AC) via Gs; AC catalyzes the production of cAMP and cAMP regulates cAMP-dependent protein kinases to open calcium ion channels. D2 receptors bind with inhibitory G protein and thus reduce the production of AC and resulting cAMP.

Several animal studies report reduced D2 receptor concentration among P rats compared to NP rats in the olfactory tubercle, caudate putamen, NAc, VTA, and the cortex.[32-34] Based on these findings, researchers have inferred a connection between the reduced D2 receptor density in the limbic system and preference for alcohol. This hypothesis has been supported by clinical studies using PET scans that report a 20% reduction in striatal D2 receptor efficiency (i.e., the ratio of D2 receptor density and affinity) in individuals with alcohol dependence compared to controls.[35-36] Another study using single-photon emission computed tomography (SPECT) found low D2/D3 receptor affinity in the left temporal cortex among individuals with Type I alcohol dependence.[37] Using whole-hemisphere autoradiography (WHA), researchers found that compared to controls individuals with Type I alcohol dependence had a 20% reduction of D2/D3 receptor affinity in the NAc region and a 41% reduction in the amygdala.[38] Results from an endocrinological study also showed decreased CNS D2 affinity in alcohol dependence.[39]

Studies about the relationship of D1 receptors and affinity for alcohol have had inconsistent results. A study reported higher striatal D1 receptor efficiency among alcohol preferring C57BL/6J mice compared to non-alcohol preferring DBA/2J mice.[40] Other studies using autoradiography techniques found no statistically significant differences in D1 receptor affinity at multiple sites in the mesolimbic and nigrostriatal regions between P and NP rats[41], between HAD and LAD rats[42] or between AA and ANA rats.[43] A clinical study using autoradiography found a 23% reduction in D1 receptor affinity in the NAc region among individuals with Type I alcohol dependence and a 14% reduction in D1 receptor affinity among individuals with Type II alcohol dependence compared to controls, but these differences showed no statistical significance.[44] Clearly, more research is needed to clarify the relationship between the D1 receptor and alcohol dependence.

4. Influence of dopaminergic system to alcohol consumption

Several studies have shown that changes in the DA system in the CNS can influence drinking behaviors both in animals and in humans. Early animal models have shown that injection of the neurotoxin 6-hydroxydopamine (6-OHDA) in the ventricle or in other brain regions destroys dopaminergic neurons. In 1975, Myers and Melchior found that CNS DA level decreased and rats showed a lower preference for alcohol after bilateral cerebral ventricle injection of 6-OHDA.[45] More recently, Ikemoto and colleagues[46] found that bilateral injection of 6-OHDA in the NAc area of alcohol-naïve rats (compared with sham-operated controls) induced a 60% decline in alcohol consumption a week later and a 30% decline three weeks later. On the other hand, Quarfordt and colleagues found that selective destruction of the NAc and tuberculum olfactorium using 6-OHDA increased drinking behavior in rats.[47] Yoshimoto and colleagues found similar results in rats after injection of 6-OHDA in the NAc[48] and ventricle.[49] The subsequent increase in alcohol consumption after injection of 6-OHDA in these studies may either be the result of direct destruction of the mechanism that results in tolerance or the result of compensatory drinking due to 6-OHDA-induced damage to DA neurons. In order to pinpoint the specific mechanism, Lanca performed fetal dopaminergic transplants of ventral mesencephalon and found increased DA levels and a 40 to 50% reduction in voluntary alcohol intake; in contrast, this effect was not observed in rats receiving a sham-operation with dopamine-poor transplants.[50] These studies clarified the inverse relationship between DA activities and alcohol consumption, supporting the hypothesis which suggests that increased alcohol intake after 6-OHDA-induced damage is compensating for the damage to DA neurons.

Research about the influence of DA receptor agonists and antagonists on alcohol consumption has had inconsistent results. Some studies find that injection of d-amphetamine (a non-specific DA receptor agonist) or quinpirole (a specific D2/D3 receptor agonist) in the NAc area can increase the frequency of alcohol-related reinforcement behaviors.[51] And local

injection of raclopride (RAC, a specific D2/D3 receptor antagonist) reduces alcohol-related reinforcement behaviors.[52] These results both support hypotheses about the positive correlation between DA activity and alcohol reinforcement. However, other studies using microinjection have found that both DA receptor agonists and antagonists can reduce voluntary alcohol intake in animal models.[52-54] For example, Samson and Hodge[52] found that administration of the antagonist RAC in the NAc reduced voluntary drinking in a dose-response fashion, while local injection of the agonist quinpirole in the VTA also reduced voluntary drinking. Kaczmarek and Kiefer found that local injection of amphetamine or RAC in the NAc both reduced ethanol intake in rats.[53] Hodge and colleagues found a bidirectional effect of quinpirole injected in the NAc area on voluntary alcohol intake: quinpirole increased alcohol intake at lower dosages and decreased alcohol intake at higher dosages.[54] The underlying mechanism of this bidirectional effect may be that presynaptic receptors are only activated when quinpirole reaches a certain concentration, after which point there is a dose-related inhibition of DA. This highlights the importance of dosage when studying the relationship between drinking and DA receptor agonists and antagonists.

5. Gene variants related to DA systems and alcohol dependence

Twin studies, linkage studies and large-sample prospective population studies have found that genetic factors play important roles in the development of alcohol dependence. Two groups of genes have been related to alcohol dependence. One group of genes encode enzymes involved in alcohol metabolism, including alcohol dehydrogenase, aldehyde dehydrogenase and cytochromes P4502E1. The second group of genes encode neurotransmitters (and the receptors for these neurotransmitters) that respond to alcohol and its metabolites, (e.g., DA, GABA, 5-HT, and opium).[55] D1, D2 and D4 receptors and DA transporter polymorphisms have been shown to play a role in alcohol dependence, but there remains controversy about the pathways via which these effects are produced. In 1990 Blum and colleagues first proposed that: "the D2 receptor A1 allele is closely related to the development of alcohol dependence". They found that the D2 receptor A1 allele was associated with a 8.7 higher odds of developing alcoholism.[56] This finding has been replicated by many case-control studies and other works have shown that gene polymorphisms that inhibit the expression of the D2 receptor are associated with increased risk of alcohol dependence.[57,58] In support of this hypothesis, a recent study found increased alcohol intake among D2L receptor knock-out mice.[59] In contrast, other studies failed to find any association between the D2 receptor and alcohol dependence.[60,61] Possible reasons for these contradictory findings include differences in sample characteristics (e.g., types of alcohol dependence, selection of controls, and race/ethnicity) and other methodological differences across studies. Parallel work with D1 receptors by El-Ghundi and colleagues found lower alcohol preference and intake among D1 knockout mice compared to wild-type mice.[62] Using a case-control design, Zhong and colleagues studied three genetic polymorphisms of D2 (TAQI A, TAQI B, -141CINS/DEL), the 48bp variable number tandem repeat (VNTR) of the 3rd exon of the D4 receptors, and the 40bp VNTR of the non-coding region at the end of the DA transporter gene 3' in a sample of Chinese Han individuals living in Yunnan province. They found that the D2 TaqIB genotype and allele frequencies were associated with alcohol dependence and that carriers of the B2 allele had a lower risk of alcohol dependence, but no differences were found for the other polymorphisms between cases and controls.[55]

6. Summary and prospect

Anatomy, physiology, pharmacology, and behavior studies have found ample evidence for the connection between the neurotensin (NT) and DA systems. A case-control study conducted by our research team[63] in a sample of Chinese Han individuals found that the GG genotype of the single nucleotide polymorphism (SNP) rs6011914C/G and the G allele and GG genotype of the SNP rs2427422A/G of the NTR1 receptor were associated with alcohol dependence; linkage disequilibrium was found between rs6090453C/G, rs6011914C/G and rs2427422A/G; and the haplotypes rs6090453C/rs6011914C/rs2427422A and rs6090453C/rs6011914C/rs2427422G were found associated with alcohol dependence.[63] These findings suggest that the NT system may affect the development of alcohol dependence via the dopaminergic system and shed some new light on the mechanism linking the DA system functioning to alcohol dependence.

Animal studies have found that selective D2 receptor agonist bromocriptine can reduce alcohol intake and acute ethanol tolerance in alcoholic rats.[64] Clinical studies also found that bromocriptine can relieve symptoms of alcohol dependence and related problems in humans.[65] In contrast, another study reported the treatment effect of tiapride, a selective D2/D3 receptor antagonist, in alcohol dependence.[66] Other double-blinded placebo-controlled studies did not find any treatment effect of either DA agonist[67] or antagonist [68] compared to placebos, and documented some serious side effects of the drugs. Given these contradictory findings, dopaminergic drugs have not been recommended for the clinical treatment of alcohol dependence. Currently, the United States Food and Drug Administration (FDA) has approved acamprosate, tetraethylthiuram disulfide (TETD, disulfiram) and naltrexone as treatment mediations for alcohol dependence and alcohol misuse. The mechanism of action of these agents is related to their effects on the CNS glutamatergic system.[69,70]

All psychoactive drugs can activate the mesolimbic DA system, but the DA system is not the only system involved in the positive reinforcement network in the NAc. Previous research about the neurobiochemisty

of alcohol dependence has focused on the DA system, but many of the findings have been contradictory. This may be related to varying methodologies, to non-linear dosage effects, to non-transferability of animal results to humans, to different target groups (most previous studies have used samples from Western countries), and to the possible confounding effects of other inter-related neurotransmitter systems. Further research aimed at clarifying the interaction between the DA system, the glutamatergic system and other neurotransmitter systems is needed before it will be possible to improve the effectiveness of interventions for preventing and treating alcohol dependence.

Conflict of interest

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多巴胺系统和酒精依赖

马慧，朱刚

摘要：酒精依赖是一种常见的精神疾病，社会危害大，疾病负担重。目前致力于酒精依赖的预防和治疗的研究取得的成果比较有限。为了进一步完善酒精依赖的治疗和预防措施，有必要对酒精依赖潜在的生物学机制进行深入探究。迄今为止，针对酒精依赖错综复杂的病因学的研究，大部分聚焦于多巴胺系统的关键作用。本综述总结了目前国内外对饮酒行为与多巴胺能系统之间关系的研究，发现研究结果并不一致，甚至相互矛盾，可能是由于方法学的差异、非线性的剂量效应、样本的选取差异以及多巴胺系统与其它神经递质系统之间可能存在交互作用等因素造成。

关键词：多巴胺，酒精依赖，神经生化，综述

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