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Mini-review

Molecular mechanisms of synaptic remodeling in alcoholism

Evan J. Kyzar[a], Subhash C. Pandey[a,b,*]

[a] Department of Psychiatry, University of Illinois at Chicago, Jesse Brown Veterans Affairs Medical Center, Chicago, IL, USA
[b] Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL, USA

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ABSTRACT

Alcohol use and alcohol addiction represent dysfunctional brain circuits resulting from neuroadaptive changes during protracted alcohol exposure and its withdrawal. Alcohol exerts a potent effect on synaptic plasticity and dendritic spine formation in specific brain regions, providing a neuroanatomical substrate for the pathophysiology of alcoholism. Epigenetics has recently emerged as a critical regulator of gene expression and synaptic plasticity-related events in the brain. Alcohol exposure and withdrawal induce changes in crucial epigenetic processes in the emotional brain circuitry (amygdala) that may be relevant to the negative affective state defined as the "dark side" of addiction. Here, we review the literature concerning synaptic plasticity and epigenetics, with a particular focus on molecular events related to dendritic remodeling during alcohol abuse and alcoholism. Targeting epigenetic processes that modulate synaptic plasticity may yield novel treatments for alcoholism.

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Contents

1. Introduction

Alcohol abuse and alcoholism represent significant public health problems that impact both the individual and society as a whole [1]. Alcoholism is defined as compulsive drug seeking behavior that interferes with normal functioning and is related to various psychiatric states such as stress and anxiety [2–7]. Additionally, alcoholism and alcohol abuse are characterized by both positive and negative emotional states [4,5]. The behavioral switch between positive reinforcement (i.e., seeking a drug for its rewarding effects) and negative reinforcement (i.e., seeking a drug in order to remove the negative emotional state associated with withdrawal) is an important aspect of the cycle of alcohol addiction [4,5]. The negative affective states (e.g., anxiety, stress, and dysphoria) that drive the negative reinforcement of addiction, along with the

* Corresponding author at: Department of Psychiatry, University of Illinois at Chicago, Jesse Brown VA Medical Center, 1601 West Taylor St (M/C 912), Chicago, IL 60612, USA. Tel.: +1 312 413 1310; fax: +1 312 996 7658.
E-mail address: scpandey@uic.edu (S.C. Pandey).

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physical manifestations of drug withdrawal, are referred to as the "dark side" of addiction [4–7].

The dark side of addiction represents a dysfunction of brain reward and emotion systems [5–7], and therefore, targeting aberrant molecular pathways in these circuitries may yield better therapeutic interventions for alcoholism and other addictive behaviors. In particular, the extended amygdala (consisting of the central nucleus of the amygdala [CeA], the bed nucleus of the stria terminalis [BNST], and a transitional zone of the nucleus accumbens [NAc] shell) [7,8] is posited to integrate stress signals in the brain with reward processing through dynamic molecular regulation leading to changes in synaptic plasticity and dendritic arborization [4,9,10]. Several molecular and cellular substrates in key brain regions play a crucial role in the development and maintenance of drug abuse and addictive behaviors [3,9–14].

Uncovering the precise molecular machinery responsible for abnormal dendritic branching and synaptic remodeling remains an important research area in the field of alcoholism. Recent evidence has implicated both genetic and epigenetic mechanisms in the control of synaptic plasticity, particularly as it relates to alcohol consumption and addiction [3,11]. In this review, we will summarize the current knowledge of molecular and epigenetic mechanisms underlying synaptic remodeling and maintenance of the "dark side" or negative affective state of alcohol addiction.

2. Synaptic plasticity and alcohol

2.1. Plasticity at the individual synapse

Drug and alcohol addiction are often characterized as a dysfunction of normal learning and memory circuits within the brain [4,11,12]. These complex processes are governed by the rapid forming and reforming of synaptic structures in particular brain regions that occur concomitantly with changes in signaling at the level of individual synapses, collectively known as synaptic plasticity [13]. At the single synapse level, synaptic transmission at a particular synapse enhances the efficacy of subsequent signaling at that same synapse in a process known as long-term potentiation (LTP) [14]. Conversely, the dampening of future synaptic transmission is called long-term depression (LTD) [15]. In addition to LTP and LTD, changes to the ultrastructure of synapses play a role in the pathogenesis of addiction through the action of several different neurotransmitter systems, particularly the mesolimbic dopamine system [16,17]. Glutamatergic and GABAergic systems are also implicated in synaptic remodeling and are affected by exposure to alcohol and drugs of abuse [17,18].

2.2. The effect of alcohol on dendritic spine formation

Modulation of signaling events at the single synapse are accompanied by the structural reorganization of neuronal dendritic spines [19], sometimes referred to as metaplasticity [16]. The observation of certain mRNA and protein transcripts, such as activity-regulated cytoskeleton-associated protein (Arc), found in recently activated synapses led to the hypothesis that specific molecular players were involved in structural synaptic remodeling [20,21]. Arc is transported to dendritic spines by actin-based motor proteins, where it modulates glutamatergic neurotransmission and structural organization [22–24]. By this process, dendrites form and re-form connections to other neurons in the surrounding area. Dendritic branching and arborization are robustly affected by many drugs of abuse, including cocaine, heroin, and alcohol [17,24], and several cellular mechanisms [1–4] have been implicated in long-lasting behavioral changes associated with drug addiction such as compulsive drug-seeking and negative affective states [4,7,12].

Alcohol exerts effects on the morphology of dendritic spines. In particular, acute alcohol administration is associated with an increase in dendritic spines in the CeA and medial nucleus of the amygdala (MeA) of rats [24]. These structural effects coincide with alcohol-induced anxiolysis and an increase in expression of brain-derived neurotrophic factor (BDNF) and Arc gene products known to play a role in synaptic plasticity [24]. Interestingly, withdrawal from chronic alcohol exposure decreases dendritic spines and Arc and BDNF expression in the CeA and MeA, leading to anxiogenesis in rats [24,25]. Withdrawal from chronic alcohol exposure also decreases dendritic arborization in the hippocampus and the NAc [26,27]. This data mimics results from postmortem studies of human alcoholics showing decreased dendritic spine density in cortical pyramidal neurons [28]. These studies support the notion of a synaptic plasticity-driven model of alcoholism.

Acute alcohol exposure provokes anxiolysis and increased dendritic spines in the amygdala, whereas continued exposure normalizes dendritic arborization and attenuates anxiolytic-like behavior. However, withdrawal from chronic or binge ethanol consumption, and especially repeated withdrawal, causes a stark decrease in the number of dendritic spines in the amygdala and other important brain regions, accompanied by increased anxiety-like behaviors. Relapse to drinking possibly normalizes dendritic spine density (Fig. 1). Notably, changes in structural plasticity are accompanied by changes in BDNF and Arc gene expression in these studies, providing a molecular framework for the structural changes seen with altered synaptic plasticity. Several studies in the field have shown that Arc directly regulates dendritic spines both in the hippocampus and amygdala [24,29]. Interestingly, increased BDNF and Arc expression leads to increased dendritic spine density in the CeA and decreased anxiety-related and drinking behavior, while decreased BDNF and Arc expression in the CeA leads to decreased dendritic spine density and increased anxiety and drinking behavior (Fig. 2) [24,25]. This cellular mechanism provides a possible explanation for many of the behavioral consequences of alcoholism, including compulsive drug-seeking and negative affective states seen during withdrawal.

2.3. NMDA receptors and alcohol-dependent synaptic reorganization

The glutamatergic *N*-methyl-D-aspartate (NMDA) receptor is known to play an essential role in both short- and long-term activity-dependent synaptic plasticity [31–33]. These receptors act as modulators for the transmission of excitatory impulses to the postsynaptic nerve terminal. Interestingly, acute alcohol exposure potently inhibits NMDA-mediated currents, resulting in less depolarization in postsynaptic neurons [34,35]. Chronic ethanol exposure, on the other hand, increases the sensitivity of NMDA receptors to glutamate, potentiating neuronal depolarization and subsequent activation [35,36]. These effects are specific to NMDA receptors targeted to the synapse, rather than extrasynaptic receptors [37] and are localized to the amygdala in rodent models [35,36,38]. Withdrawal from alcohol produces robust anxiety-like behavior which is reversed upon administration of a glutamatergic antagonist in the amygdala [39]. This data suggests that the glutamatergic system and NMDA receptors are at least partly responsible for the anxiety-like behavior seen during alcohol withdrawal. Additionally, exposure to chronic ethanol caused a decrease in dendritic spine density in medium spiny neurons in the nucleus accumbens (NAc), which was associated with an increase in NMDA receptor NR1 subunit expression (discussed further below) [26]. Other studies showed the decrease in NAc spine density, particularly in "long thin" spines, was accompanied by a decrease in post-synaptic density-95 (PSD95)-positive and tyrosine hydroxylase (TH)-positive immunostaining in rats undergoing