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Neurobiology of substance use disorder-recent advances

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Abstract
Changes in neurocircuits, molecular changes and the genetic variations those are responsible for the neuroadaptations mediate the development of addiction. Addictive drugs can trigger epigenetic mechanisms that modulate the expression of genes implicated in neuroplasticity ultimately perturbing the intracellular level of key proteins, and modifying neurotransmitter signaling in various neuronal circuits in the brain. The resultant behavioural dysfunctions in addiction reflect the emergent property of complex systems that are disrupted at multiple, interacting levels.

Keywords: addiction, neurocircuits, molecular changes, genes

Introduction

Drug addiction has been conceptualized as a disorder that moves from impulsivity to compulsivity in a collapsed cycle of addiction [1]. In individuals with substance use disorders, periods of chronic substance use are invariably followed by periods of abstinence and withdrawal. Periods of withdrawal from drug use are followed by instances of relapse, whereby drug-seeking and drug-taking are reinitiated by various trigger factors, both internal (e.g., stress states) and external (e.g., previously drug-paired environmental cues) to the individual [2].

Mechanisms of addiction can be understand by various animal models [3]. While no animal model of addiction fully imitates the human condition, animal models do permit investigation of the process of drug addiction and how the nervous system adapts to drug use [4].

Neurocircuits of Reward and Anti Reward

Running toward pleasure by using a drug leads to a heightened dopamine influx from the midbrain to the ventral striatal areas (part of the brain's pleasure centre) and the prefrontal cortex (the thinking part) that leads to the conscious experience of pleasure [5].

The concept of reward or positive reinforcement as the initial driving force is examined against the concept of anti-reward or negative reinforcement. Two important biological systems in the concept of negative reinforcement are neuropeptide Y (NPY) and corticotropin-releasing factor (CRF) [6].

NPY has been described as a stress buffer, working in opposition to the stress-promoting properties of CRF [7]. With repeated drinking episodes, the delicate balance between the anxiolysis brought about by alcohol and NPY, and the anxiogenic effects of CRF, are in the long run reversed. As a result, CRF/glutamate tone is heightened (glutamate is the main excitatory neurotransmitter), and NPY/GABA is reduced (GABA is the main inhibitory brain transmitter). The anxious dysphoria that arises in the period between drinks is relieved only momentarily by further drinking, thereby shifting the motivation from a hedonic (pleasure-seeking) one to the prevention of further stress and dysphoria [6, 7].

Impulsivity to Compulsivity

Various neuroimaging studies have revealed generalized prefrontal cortex (PFC) dysfunction in drug-addicted individuals. Dorsal PFC has been predominantly implicated in top-down control and meta-cognitive functions, the ventromedial PFC in emotion regulation, and the ventrolateral PFC and lateral orbitofrontal cortex (OFC) in automatic response tendencies and impulsivity. With chronic substance abuse, Dysfunction of these PFC regions occur that leads to shift from impulsive to compulsive use of drugs [8].

Synaptic Plasticity and Structural Changes in Addiction

Drugs of abuse disrupt the strength of excitatory synapses by tapping into traditional mechanisms of synaptic plasticity, including long- term potentiation (LTP) and long-term depression (LTD) [9]. Synaptic plasticity is controlled pre-synaptically through the regulation of glutamate release and post- synaptically through the insertion or removal of AMPA or NMDA glutamate receptors and drugs of abuse interfere with these processes [10]. Changes in corticofugal glutamatergic input to the striatum associated with repeated drug use eventually lead morphological changes in dendritic spine density [11]. The end result of this change can apparently be manifested as either an increase or a decrease in spine density but is likely associated with more plastic spine responsiveness to the increased glutamate release [12].

Neuro-Circuits Responsible for Relapse

Conditioned Cue-Induced Relapse

With repeated drug use, events and stimuli associated with drug use become associated with reward, or reinforcing also [13]. Enhancing dopamine levels in the amygdala during cue presentation is seen that leads to potentiate cocaine-seeking [14]. The dorsal medial prefrontal cortex, the lateral orbitofrontal cortex, or the nucleus accumbens core subregion also significantly attenuates cue-induced cocaine-seeking [15].

Drug-Primed Reinstatement

Small doses of an abused drug can initiate subjective states of drug desire that prompt more drug consumption again. Except amygdala, other regions that are necessary for cue-induced reinstatement are also necessary for drug-primed reinstatement, including the prelimbic cortex, nucleus accumbens core, and ventral pallidum [16].

Stress-Induced Reinstatement

Chronic administration of drugs with dependence potential dysregulate both the hypothalamic-pituitary-adrenal (HPA) axis and the brain stress system mediated by corticotropin-releasing factor (CRF) [17]. An activated brain stress responses with activated amygdala CRF during acute withdrawal from all major drugs of abuse [18].

Changes at Molecular level

In the nucleus accumbens and other dopaminergic neurons, most drugs of abuse induce immediate early gene expression, including the transcriptional regulators c-fos and NAC-1. Expression of immediate early genes more closely tied to synaptic activity is also upregulated, including narp, Arc, and Homer1a [19]. These proteins initiate the sequelae of cellular changes that lead to enduring neuroadaptations. For example, the induction of cAMP response element binding protein (CREB) by stimulating D_1 dopamine receptors not only stimulates c-fos but also activates the synthesis of ΔFosB, a transcriptional regulator that endures for days to weeks after the last drug exposure [20].

BDNF is generally increased by acute drug use and appears to undergo further elevation during drug abstinence [21]. Upregulated BDNF promotes vulnerability to drug-seeking, including upregulation in the amygdala, ventral tegmental area, and nucleus accumbens [22]. However, an opposite role for BDNF is also seen which reduced vulnerability to cocaine-seeking [23]. while BDNF undoubtedly contributes to the enduring neuroplastic changes produced by repeated drug use, BDNF-induced changes may be both pro addictive as well as compensatory in nature

Genetic Factor

During the critical developmental period, individuals are exposed to an environment that encourages substance use. Once exposed to the psychoactive substance, their genotypes confer vulnerability to its rewarding properties and/or insensitivity to its negative effects so that heavy use can lead to the development of dependence [24]. Twin studies provide substantial evidence that genetic factors contribute to the etiology of substance use disorders (SUDs) [25]. Genetic risk factors for SUD also a part of a broad genetic liability to "externalizing" disorders, which includes conduct disorder, antisocial personality and probably personality traits related to poor impulse control and sensation seeking [26].

The mu-opioid receptor gene (OPRM) can give rise to 2 genetic variants. One of those, the Asp40 allele variant, confers an increased functional activity to the mu-receptor, elevating its response to endogenous opioids and also to the synthetic opioids and alcohol [27]. Individuals with that genetic variant will have a heightened response to the euphoric effects of alcohol and opioids. So increased receptor sensitivity will lead to a rapid onset of tolerance.

Genes for several nicotine acytyl choline receptor (nACh) proteins drive different aspects of the multistep process of nicotine addiction. The influence of nACh proteins on nicotine addiction mainly focused on the α_4 and β_2 subunits. These are the most abundant and widely distributed nACh subunit proteins in the brain. Researchers have implicated the genes-located on chromosome 15-for the α_3, α_5, and β_4 proteins [28] in early initiation of smoking, the transition to dependence, and two smoking-related diseases: lung cancer and peripheral arterial disease [29]. Investigators have also found that whether or not a person experiences extreme dizziness upon first trying cigarettes, as well as his or her risk of addiction, depends in part on the genes-on chromosome 8-for the α_6 and β_3 proteins [30].

Recent animal studies have shown that prenatal exposure to cigarette smoking is associated with specific brain changes and behaviours later in adolescence, some of which could be traced back to methylation events along specific genes such as BDNF [31].

Initial sensitivity to alcohol is strongly and inversely related to risk for alcohol dependence [32]. However, the only variants that affect sensitivity to alcohol and have known functional impact on alcohol dependence risk are in genes encoding the alcohol dehydrogenase (ADH) and aldehyde dehydrogenase 2 enzymes [33, 34], and they confer substantially reduced, rather than increased, risk for alcohol dependence by causing aversive reactions to ethanol. GABAA subtype receptors are also sensitive to ethanol [35]. GABRA2 is involved in the predisposition to alcohol dependence through a general externalizing-disorder pathway.

Neuroimmune Signaling, Drug Abuse, and Stress

Stress and psychoactive substances activate regulatory protein nuclear factor k–light-chain enhancer of activated B cells (NF-kB) that is expressed in large amounts in monocytes and microglia. Microglia and astrocytes undergo multiple stages of activation and express major histocompatibility complex (MHC) on their surface. Alcohol- induced glial activation is associated with increased expression of innate immune genes, including increased expression of the chemokine monocyte chemoattractant protein-1 (MCP1); the cytokines tumor necrosis factor-a (TNFa), interleukin-1 b (IL-1b), and interleukin-6 (IL-6). The alcohol-induced activation of glial innate immune genes increases neuronal hyperexcitability in the cortical areas by excess activity of glutamate [36].

Conclusion

"Between stimulus and response there is a space. In that space is our power to choose our response. In our response lie our growth and our freedom."(Viktor E. Frankl.). A common target that emerges for prevention and treatment is needed to balance the critical space that exists "between stimulus and response" and that becomes increasingly

disrupted as the severity of a substance use disorder deepens.

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Declaration of interest
None.

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