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Stress and its Vulnerability to Addiction

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Abstract

Stress is a normal and unavoidable part of our life. Numerous studies have linked stress with the addiction to drugs of abuse. Researchers have revealed that there is overlap between the neurocircuits that respond to drugs and those that respond to stresses. Like illicit drugs, stress can increase the dopamine release in the nucleus accumbens, a component of brain reward circuit. The release of dopamine in the nucleus accumbens is considered to be one of the major substrates of the addictive properties of drugs. In this article an attempt has been made to understand the cellular mechanism by which stress triggers the addictive behaviours acting on the brain reward circuit.

Keywords: Stress; Glucocorticoid; Dopamine; Nucleus accumbens; Addiction

Introduction

Stress is considered as an important risk factor for the development and relapse of addictive behaviors. Adverse environmental factors such as early life stress, child maltreatment as well as adult adversities increase the risk of addiction. Stress experiences can either be emotional or physiological. Emotional stressors may arise in the form of loss of good relationships, death of a beloved one, interpersonal conflicts etc. Physiological stresses may include deprivation of food and sleep, hunger, drug withdrawal etc. [1]. It is considered that individuals become addicted to drugs to cope with stress and to reduce the tension [2]. It has been seen that adolescents facing high recent negative life events show increased level of drug uses [3,4]. Furthermore, an increased association between childhood sexual and physical abuse has been observed with increased drug uses and abuses [5,6]. One study revealed that during a period of more than two years, the rate of occurrence of various stresses such as death of relatives, family problem, legal problem, occupational and other problems in opium addicts was statistically higher than normal subjects [7]. Our brain has a 'reward circuit' that denotes mesolimbic system which includes ventral tegmental area (VTA), in the midbrain and comprises dopamine (DA) secreting neurons that project to nucleus accumbens (NAc), amygdale (Ag), hippocampus (H) and to prefrontal cortex (PFC). Rewarding and reinforcing properties of the abusive drugs involve the activation of VTA dopaminergic neurons to release DA onto NAc and PFC [8]. It has been indicated that mesolimbic DA reward pathway is strongly responsive to stresses [9]. In this present article we will make a discussion how this reward circuit operates to develop addictive behavior and how does the stress increase the vulnerability to addiction utilizing this pathway.

Addiction Circuitry and its Vulnerability to Addiction induced by Stress

Let us exemplify the neural mechanism in operation during the development of addiction owing to repeated uses of psychostimulants like cocaine, amphatamine etc. [8]. Psychostimulants increase the DA in the synapse formed by the VTA dopaminergic neuron on their targets like PFC, NAc etc. As the activation of the VTA DA neurons are driven by glutamate, strengthening of glutamatergic synapses of VTA neurons increases the DA release in the targets. Cocaine acts locally with VTA to induce long-term potentiation (LTP) by activating D5 receptors on membrane by DA to activate N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Repeated cocaine intake also causes the increase the DA concentration in the VTA DA neuron-PFCsynapses. DA promotes LTP in PFC cells by stimulating D1 receptors and thereby inactivating the inhibitory γ-aminobutyric acid (GABA) receptors or recruiting excitatory GluR1 containing AMPA receptors. Potentiated PFC can activate the VTA DA neurons to release DA in NAc. The major cell type in NAc is GABA-ergic medium spiny neurons (MSNs) that inhibit ventral pallidum (VP), the main executor of the motor activities related to addictive behaviors [9].

Repeated cocaine exposure can activate D1 receptors of MSNs and ultimately via an intracellular signaling cascade the functions of AMPA receptors in MSNs are declined. As a result these MSNs are less excited to release GABA on VP. The disinhibited VP in turn executes reward related activities. Another type of MSN in NAc that co-release GABA and encephalin makes synapse with VP. These MSNs can be excited

by PFC glutamatergic neuron to co-release GABA and encephalin. Encephalin in turn binds to the presynaptic mu-opoid receptors that are coupled to inhibitory G-proteins. Activated inhibitory G-proteins via an intracellular cascade mechanism cause the hyperpolarization of these MSNs resulting in the blocade of their GABA release and the subsequent disinhibition of VP to execute reward related behaviors. Potentiation of PFC owing to repeated cocaine exposure forms reward related memories in this brain region. As a consequence merely the observation of a reward related cue may cause the excitation of the potentiated PFC glutamatergic neurons to release glutamate on these MSNs in NAc that become hyperpolarized by the activities of encephalin and allow to execute reward related addictive behaviors via the disinhibition of VP.

Most stressors exert their effects on the hypothalamic-pituitary-adrenal (HPA) axis that release glucocorticoid (GC) [10], denoted as cortisol and corticosterone in human and rodents respectively [11], in circulation. GC released after acute stress exerts the feedback inhibition of its own synthesis [12]. However, chronic stresses induce the hyperactivity in HPA axis resulting in elevated level of GC in circulation [13]. The HPA axis activation causes the release of corticotrophin –releasing factor (CRF) from the hypothalamus which stimulates the pituitary to release adrenocorticotropic hormone (ACTH) that acts on the adrenal cortex to release GC [14]. It has been seen that exposure of stress and increased GC level enhances the DA release in NAc [15]. Furthermore suppression of GC by adrenalectomy reduces the extracellular DA both under basal condition and in response to stress and psychostimulants [16]. Stress-induced GC also enhances the glutamate activity in VTA that in turn increases the activities of DA neurons [17]. Human brain imaging studies also revealed the stress-induced increased level of cortisol was associated with DA accumulation in the striatum [18]. Thus it is evident that stress-induced GC causes the accumulation of DA in the major components of the reward circuit as that occurs during the psychostimulant intake indicating the utilization of the common pathway that gives rise to addictive behaviors. It has been seen that like the exposure to drugs of abuse, acute swim stress increases the AMPA/NMDA ratio of excitatory synapses on VTA dopaminergic neurons causing the excitation of these cells to release DA on its target [19]. GC can increase the DA synthesis through their facilitatory action on tyrosine hydroxylase and may also reduce DA metabolism and clearance from the synaptic cleft by decreasing the activity of metabolizing enzymes such as monoamine oxidase [20].

It indicates that chronic stresses result in similar outcome i.e. increase in the level of DA in brain reward circuit as that happens as a consequence of intake of an abusive drug and increase the vulnerability to addiction. It has also been reported that stress plays an important role in the relapse of addictive behaviors. Experimental evidences indicated that exposure of animals to aversive experiences caused the reinstatement of their drug-seeking behavior [21]. Persons who quit smoking and subsequently relapsed often also reported that their relapse to smoking was triggered by stressful experiences [22]. GC receptors (GR) are present throughout the mesolimbic reward pathway [23]. As it is mentioned that GC augments DA release in the NAc, it is not surprising that exposure of GR antagonists exhibited substantial decrease of DA in NAc [24]. Furthermore, GR antagonists when are locally injected into VTA decrease the morphine induced increase in locomotor activities [24]. In addition to glucocorticoids, CRF released during HPA axis activation can regulate VTA functions. The paraventricular nucleus of the hypothalamus sends CRF-positive projections to the VTA . While CRF-containing projections form both glutamatergic and GABAergic synapses, it appears that CRFcontaining synapses on VTA dopaminergic neurons are primarily glutamatergic [19]. Thus CRF can contribute to modulate VTA DA neurons via the potentiating glutamate release and excitatory transmission. As a result CRF can facilitate the DA signaling in the NAc as it is done by drugs of abuse [14].

Discussion

It is clear that stress plays an important role in the initiation and relapse of the drug seeking behaviors. Our brain reward circuit responds to both stresses and illicit drugs and induces DA release in the NAc which is needed for drug seeking behaviors. Stress induced activation of HPA axis and subsequent release of CRF and GC allow these hormones act on their receptors on VTA to stimulate DA release. As DA release is thought to mediate incentive salience attribution, this priming mechanism probably makes someone who is under stress much more vulnerable to addiction.

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