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A Systematic Review on Pharmacological Significance of Adenosine-2 A And Dopamine-D_2 Receptor Interaction In Drug Addiction

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A B S T R A C T

Addiction to a drug candidate is defined as its excessive intake that can be rewarding and reinforcing to an individual. Drug addiction can also develop socio-economical challenges which can hinder the overall growth of any country. Therefore, mechanism of development of drug addiction is a prime requirement in the current era. Recently, it has been proposed that allosteric receptor-receptor interactions in homo- and heteroreceptor complexes may form the molecular basis of drug addiction. It has been reported that cocaine abuse can alter the adenosine A2AR-dopamine D2R hetero complexes and their receptor-receptor interactions and thereby induce neural plasticity in the basal ganglia. It has also been suggested that the composition and allosteric plasticity of these complexes in the ventral striatopallidal neurons may play a significant role in the genesis of drug addiction. It has also been documented that adenosine 2A receptor (A2AR) agonists can reduce cocaine reward and cocaine seeking mainly through activation of antagonistic allosteric A2AR-dopamine D2R (D2R) interactions in A2AR-D2R heteroreceptor complexes. Additionally, it has been suggested that cocaine self-administration can reorganize A2AR and D2R into increased A2AR-D2R heteroreceptor complexes in the nucleus accumbens shell associated with increases in the D2R-sigma1R heteroreceptor complexes in the brain. This reorganization can contribute to the demonstrated anti-cocaine actions of A2A receptor agonists and the putative formation of A2AR-D2R-sigma1R heterocomplexes. In conclusion, adenosine A2AR-dopamine D2R interaction perhaps play a significant role in the development of drug addiction and their modulation may contribute towards the management of drug addiction

KEYWORDS:

Drug addiction, Adenosine, Dopamine, A2AR-D2R complex.

1. INTRODUCTION

Drug addiction is defined as excessive intake of a drug candidate that can be rewarding and reinforcing to an individual. Drug addiction is a serious brain disorder with somatic, psychological, psychiatric, socio-economic and legal implications in the developing as well as developed countries [1]. Illegal (e.g., psychostimulants, opioids, cannabinoids) and legal (alcohol, nicotine) drugs of abuse create a complex behavioral pattern composed of drug intake, withdrawal, seeking and relapse. One of the hallmarks of drugs that are abused by humans is that they have different mechanisms of action to increase dopamine (DA) Neurotransmission within the mesolimbic circuitry of the brain and indirectly activate DA receptors. Among the DA receptors, D(2) receptors are linked to drug abuse and addiction because their function has been proven to be correlated with drug reinforcement and relapses. The recognition that D(2) receptors exist not only as homomers but also can form heteromers [2], such as with the adenosine (A)(2A) receptor, that are pharmacologically and functionally distinct from their constituent receptors, has significantly expanded the range of potential drug targets and provided new avenues for drug design in the search for novel drug addiction therapies [3] Adenosine-dopamine interactions in the central nervous system (CNS) have been studied for many years in view of their relevance for disorders of the CNS and their treatments. The discovery of adenosine and dopamine receptor containing receptor mosaics in the striatum opened up a new understanding of these interactions. Initial findings indicated the existence of A(2A)R-D(2)R heterodimers and

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A(1)R-D(1)R heterodimers in the striatum that were followed by indications for the existence of striatal A(2A)R-D(3)R and A(2A)R-D(4)R heterodimers [4]. It has also been documented that antagonistic allosteric A(2A)-D(2) and A(1)-D(1) receptor-receptor interactions take place in striatal A(2A)R-D(2)R and A(1)R-D(1)R heteromers. Hence, the aim of the review is to bring current focus on A(2A) receptors, their physiology and pharmacology in the central nervous system, and to discuss the therapeutic relevance of these receptors with respect to dopamine receptors during drug addiction

2. MATERIAL AND METHODS

Pharmacological significance of dopamine and its receptor in drug addiction:

Dopamine plays an impotent role in different stages of drug addiction. [5] Physiological functions of dopamine are mediated through different type of dopaminergeic receptor, which are divided into two subgroups [6]. It is well known that dopamine is involved in wide range of physiological functions and its dysfunction leads to neurological disorders [7]. Several researchers have been strongly suggested that the dopamine is playing an important role in drug addiction. Brancato at el. have reported that D2 receptor is involved in the acetaldehyde induced addiction behavior in rodents [8]. Most of the abused or addicted drugs cause stimulation of D2 receptor in the dorsal and ventral straitum region of the brain and mediate the sensitizing and rewarding effect [9]. Partial agonist of dopamine (Aripiprazole) decreases the alcohol drinking behavior in human. It is found that mRNA of D3 receptor expression is increased in the cocaine cue conditioned locomotion [10]. Additionally, postmortem studies of human body suggested an increase in the number of D3 receptor in the specific area of brain with overdose of cocaine [11]. The BP897, partial agonist of D3 produces critical dosage subordinate diminishment in the quantity of reactions for cocaine [12]. In support of above study one more investigation has suggested that BP897 decreases the cocaine seeking behavior in rats [13]. These observations clearly demarcates the fact that dopamine plays a significant role in the genesis and regulation of drug addiction through its receptors in the brain.

Pharmacological significance of adenosine and its receptor in drug addiction:

Adenosine is an endogenous purine nucleoside formed as a byproduct of metabolism of adenosine triphosphate (ATP) that is found abundantly in the central nervous system. It is an indispensable chemical which exerts distinct function in the brain through different types of A1-A3 adenosinergic receptor [14]. Adenosine A1 and A3 receptors act via decreasing the cAMP through an activation of Gi proteins-mediated inhibition of adenyl cyclase, whereas A2A and A2B receptors activations stimulate adenyl cyclase and increase cAMP production [15]. The adenosine A1 agonist negatively affects the binding of dopamine to its high affinity D1 receptor [16]. Adenosine influences the dopamine and glutaminergic neurotransmission in the straital region of brain [17]. In a one report Fillip et al. had reported that the A2a receptor agonist can decrease the dopamine transmission in GABA neuron, while A2a antagonist increases the dopamine release[3]. Activation of A2a receptor decreases the affinity of dopamine receptor agonist [18]. Motor activation effect of dopamine is increased by the adenosine antagonist while agonist decreases the Motor effect induced by dopamine [19]. In another study it has been suggested that the stimulation of A2a receptor also decreases the cocaine sensitization [20] and blocks the restoration of cocaine seeking [21]. Thus, it can be assumed that adenosine and its receptors may modulate the activity of dopamine activity in the regulation of drug addiction

3. RESULTS AND DISCUSSION

Adenosine 2A and Dopamine 2 Receptor interaction:

The molecular studies have already been proposed that dopamine and adenosine receptors are subtypes of G protein coupled receptor family. Effect of dopamine in central nervous system are mediated through postsynaptic D1 and D2 receptor whereas adenosine A1 and A2a receptor are also present on the same neuron to counter act the excessive stimulation of dopamine receptors produced by the abused Drugs. Abused drug stimulate the release of dopamine and binding of dopamine at D2 receptor decrease the activity of adenylate cyclase. Adenosine is a well known modulator of dopamine. A2a receptor exerts tonic inhibitory control over D2 receptor signaling inside the straitum. Thus, A2a receptor activation diminishes the dopamine binding at D2 receptor and this decrease in dopamine binding is mediated by heteromeric receptor complex[22].

Brown and short have reported that among all these four types of receptor only A2a receptor is involved in reward-related processes[23]. The A2a is G- protein coupled receptor and highly expressed in straitum and lower level is also found in other region of brain such as hippocampus and cerebral cortex. Activation of A2A receptor increases the release of various neurotransmitters and also modulates the synaptic plasticity and excitability of neurons. Membrane-membrane receptor interaction was first time reported by the agnati and fuex and latter on different scientist have discovered several information about receptor-receptor heteromers

[24]. A2A receptors frame homodimers, as well as interface with different receptors, such as A1, CB1, D2, D3 and metabotropic receptor to shape heteromers [25]. A2A are the major neuromodulator receptor that performs baffling impact on D2 receptor [26]. As previously mention that the cocaine decreases the expression of A2A-D2 heteromers. Large numbers of evidences have proven the existence of A2a-D2 heterodimers receptor in straitopallidal GABA neuron where activation of A2aR decreases the binding of D2 receptor [27]. First time Ferry et al. has demonstrated the heteromeric interaction between A2A-D2 receptor in which they have found that the stimulation of A2A receptor decreases the affinity of D2 receptor[28]. Feree et al. (1997) have shown that A2a and D2 receptor are present on the same neurons in striatum and provide the anatomical basis for functional interaction of A2a-D2[28]. Recent studies have shown that A2a-D2 receptor mediated signaling antagonistically interact in striato-pallidal GABA neuron to regulate the cocaine and food seeking behavior [29].

Neial et al have observed that the density of A2a receptor increased in the nucleus accumbus after long term use of cocaine self administration [30]. A2a agonist produced anti cocaine action on A2a-D2 receptor heteroreceptor complex in the ventral straitum by decreasing the promoter recognition site in D2 receptor through allostric receptor-receptor interaction. Moreover, one of another study also showed that A2aR significantly inhibit the cocaine induced reward and seeking behavior through A2a-D2 antagonistic receptor interaction. Wydar et al. have reported that the A2a receptor is also involved in the modulating of the goal-maintained behavior.

Hence, based on the review it can be concluded that adenosine A2AR-dopamine D2R interaction perhaps play a significant role in the development of drug addiction and their modulation may contribute towards the management of drug addiction.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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