



A Novel Perspective on Dopaminergic Processing of Human Addiction

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Abstract

Converging evidence from clinical, animal, and neuroimaging experiments suggests that the addictive behavior is associated with dysregulated dopamine neurotransmission. The precise role of dopamine in establishment and maintenance of addiction however is unclear. In this context animal studies on the brain reward system and the associative memory processing provide a novel insight. It was shown that both processing involve dopamine neurotransmission and both are disrupted in addiction. These findings indicate that dysregulated dopamine neurotransmission alters the brain processing of not only the reward system but also that of the memory of association between an addictive substance and reward. These alterations lead to maladaptive motivational behavior leading to chemical dependency. This concept however is based mostly on the data obtained in laboratory animals because of the paucity of human data. Due to lack of a reliable technique to study neurotransmission in the live human brain, it has been a problem to study the role of dopamine in human volunteers. A recently developed dynamic molecular imaging technique however, provides an opportunity to study these concepts in human volunteers because the technique allows detection, mapping and measurement of dopamine released in the live human brain during task performance.

It is known for the past several years that dopamine is involved in addictive process. Its precise role however, remains uncertain because of the lack of clarity on neurocognition of addiction. Two of the influential models of addiction appear to have divergent views on the neurocognition. The hedonic homeostasis model suggests that addicts require a higher level of the brain dopamine to feel rewarded [1]. It suggests that increased mesolimbic activation caused by initial drug use hyper-activates the reward system and up-regulates set point of hedonic homeostasis. Because of the up regulation the brain needs to maintain a higher level of dopamine, forcing individuals to seek drugs that raise dopamine levels. An alternate model, the associative memory model, suggests that addiction is primarily a cognitive disorder in which associative memory is pathologically subverted [2]. Because of this subversion, the reward associated with an addictive substance acquires motivational value and initiates drug-seeking behavior. Even though both models suggest that the dopamine system is dysregulated in addiction, it appears that the two models have different views on how altered dopamine neurotransmission leads to addiction. The hedonic homeostasis hypothesis assumes that addicts need higher levels of dopamine to activate the reward system and associative memory hypothesis suggests that the altered levels of dopamine impairs processing of associative memory. The two assumptions however may be complementary because as discussed in the following paragraphs, processing of both, associative memory and reward is dependent on dopamine neurotransmission. Thus, a dysregulated dopamine system is expected to impair both of these functions.

The role of dopamine in reward processing has been extensively studied in laboratory animals [3,4]. These studies have found that the reward system is regulated by dopamine released in the mesocortical pathway. It has been shown that delivery of award is associated with short phasic bursts of dopamine. These bursts disappear when the reward is predictable, and reappear if it is better than expected. If reward is withheld, the tonic release is suppressed at the expected time of delivery. Thus, changes in the phasic and tonic release of dopamine signal the nature of reward and allow the brain to make decisions based on the reward quality. Some of the findings of animal experiments are consistent with observation of molecular imaging experiments on healthy volunteers. In these experiments the binding potentials (BP) of dopamine receptor ligands measured under the baseline condition

were compared with those measured during performance of a reward task. The comparison revealed that the BP is reduced (suggesting increased dopamine release) in the striatum in a number of task conditions involving reward [5]. However, these results need to be verified because using a more sensitive single scan dynamic molecular imaging technique; we observed dopamine release in the same striatal areas in an unrewarded task [6]. Additionally, while these experiments found activation both in the dorsal and ventral striatum, in animals reward is processed primarily in the ventral striatum [3]. Thus, if molecular imaging data are verified, a major difference in dopaminergic processing of human and animal reward systems could be revealed. It will have implications on neurocognitive models of addiction because these models are based on animal data.

Associative memory has also been studied both in animals and in human volunteers. These studies have found that repeated paired delivery of a stimulus and reward sensitizes the neural system [7]. Because of this sensitization behavioral response to a previously exposed drug increases significantly when it is administered in the same cage where the drug was previously delivered. It appears that the animal makes an association between the environment (cage) and drug. It was also shown that this associative context acquires motivational significance after repeated pairing of the drug and environment [8]. Due to this motivation rats develop conditioned place preference and spend more time in the location where they received drug. The place preference therefore suggests establishment of an association between the drug and place of delivery. The brain area where this association

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is processed is not known but the nucleus accumbens (NAc) appears to be one of the possible locations. Experiments have shown that both, psychostimulants and non-stimulant addictive drugs increase dopaminergic activity in the NAc in rats [9]. Since increased dopamine concentration in this area (along with prefrontal cortex) is observed also during conditioned learning, it appears that the drug-induced dopamine release in the NAc represents learning of the association between drug and drug related cues. Because of this association, cues are known to trigger dopaminergic response similar to the one triggered by reward itself. Thus in rats, after a smell is repetitively and predictively paired with food, increased concentration of dopamine is observed in the core of the NAc and in the frontal cortex even when these stimuli are presented without food reward [10]. The NAc however does not appear to have this role in primates. In monkeys its activities are more closely associated with the reward prediction error [3] and in healthy volunteers tasks that require association activate dorsal striatal structures [6,11-13]. In another experiment dopamine release in this area was observed in cocaine addicts when they were shown videos portraying people smoking cocaine [14]. These observations indicate that in the human brain dopamine of dorsal striatum is involved in the processing of association between a cue and a reward [15]. Further evidence of dopaminergic involvement in associative process comes from pharmacological studies. These studies have demonstrated that blockade of D1 receptors prevents formation of an association between drug and its environment and its agonists enhance acquisition of conditioned response [16].

Thus, dopamine influences addictive process at multiple levels. It was suggested that in the ventral striatum it facilitates acquisition of drug seeking behavior and in the dorsal striatum, dopamine helps transition of this behavior to addiction [8]. Evidence suggests that the motivational aspect of addiction is processed in the NAc. Therefore, when its dopamine receptors are blocked, the motivation is reduced in animals [17]. The agonists on the other hand, enhance motivation [18]. Interestingly, lesion of the NAc blocks motivation for drugs but do not affect motivation for food reward. It therefore appears that the NAc regulates processing of only secondary motivational stimuli - the stimuli that acquire motivational values by associative learning [19]. This function is partly controlled by input from the amygdala where emotional and motivational significance of stimuli is processed. The dorsal striatal structures are also involved in processing of dopamine-dependent associative memory. In these structures, dopamine modulates activity of the tonically active neurons, which regulate mnemonic functions of the striatum. Enhanced dopamine activity in the dorsal striatum therefore improves memory. As a result, animals perform better in conditioning experiments if they receive amphetamine in the caudate after the training [20].

The data acquired in animal experiments however do not fully explain human addiction because of specific social, cultural and psychological issues that are associated with addictive behavior. However human studies also suggest dysregulated dopamine neurotransmission in addiction. These studies have found that in chemical dependent individuals the striatal and prefrontal activities are altered both at the baseline and during exposure to drug or drug-related cues [14]. The orbitofrontal cortex in particular shows strong abnormal activity in addicts, probably because of its involvement in the processing of psychosocial cues, which are known to modify addictive behavior and considered important trigger for relapse. Irrespective of the trigger however, relapse is dependent on the level of dopaminergic activity. Modeling experiments suggest that a low level of phasic

activity (indicated by increased frequency and duration of pauses between phasic dopamine release) reinstates suppressed memories of association between the cue and drug reward leading to relapse [21].

Further, the observation suggesting dopaminergic processing of associative learning in animals, discussed above, is consistent with the findings of our molecular imaging experiments. In these experiments we found dopamine release in the striatum of healthy volunteers during performance of tasks that require establishment of an association between a stimulus and motor response [6,12,13].

Future Perspective

It is clear from the above discussion that dopamine influences addictive behavior by altering cognitive processing associated with memory and reward. However most of the data discussed were obtained in laboratory animals. The data on the role of dopamine on human addiction is extremely limited because of the lack of a reliable technique to study neurotransmission in the live human brain. However, recent advances in dynamic molecular imaging technique implemented in our laboratory [6,11-13,22-26] and elsewhere [27] has allowed use of these techniques for detection, mapping and measurement of acutely released dopamine. Using this technique we detected, mapped, and measured dopamine released during processing of cognitive, emotional, and behavioral tasks [6,11-13,22-26]. There is therefore a need to use dynamic molecular imaging technique to acquire data on human addiction and to examine the role of dopamine neurotransmission.

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