

Can Chronic Consumption of Caffeine by Increasing D2/D3 Receptors Offer Benefit to Carriers of the DRD2 A1 Allele in Cocaine Abuse?

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The reinforcing properties of mesolimbic dopamine release caused by cocaine use disorder (CUD) are well known [1] and carriers of the DRD2 A1 allele due to hypodopaminergia (30 - 40 percent less DRD2 receptors) have significant psychostimulant risk [2,3]. The Adenosine system; important in regulating the neuronal activity associated with the sleep-wake cycle is another mechanism that may be involved in regulating DA release [4]. One animal study set out to examine the role of adenosine in cocaine-induced DA release. In order to denote a response curve increasing doses of caffeine, cocaine, and their combination, and an adenosine A1 antagonist 8-cyclopentyl theophylline (CPT), were used alone and in combination. Real-time images of the drug-induced surge of DA release *in vivo*, in a freely moving animal, were captured by the Broderick Probe biosensor, to denote a response curve of the combinations. Caffeine and cocaine were shown after administration of the low dose (2.5 mg/kg cocaine and 12.5 mg/kg caffeine) to moderately block the increased release of DA and after administration of the high dose (10 mg/kg cocaine and 50 mg/kg caffeine), dramatically, suggesting neuroprotection [5].

When administered in combination CPT and cocaine showed a decreased DA surge. Thus, protection against the cocaine-induced DA release was shown to occur with low and high doses of a nonselective adenosine antagonist, caffeine, and moderate doses of a selective adenosine antagonist, CPT. The significant interaction between adenosine and DA release demonstrated in this study suggests therapeutic options for cocaine addiction and disorders associated with DA dysfunction. In this way, caffeine can block the acute DA release effects of cocaine and would have extinction benefits just like other FDA DA blocking agents. However, this blocking effect on DA release by Caffeine in the long-term would-be counter-intuitive [5,6].

Worldwide caffeine is the most consumed psychoactive substance in the world is used to enhance alertness and promote wakefulness like drugs (stimulants and modafinil). Caffeine is an adenosine A2A receptors (A2AR) agonist [4] that enhances neuronal dopamine (DA) signaling.

At the doses consumed by humans, the question is does caffeine modulate the postsynaptic functions of DA. The [(11)C] raclopride (DA D2/D3 receptor radioligand sensitive to endogenous DA) was used for Positron emission tomography (PET) to assess whether caffeine increases DA release in striatum in 20 healthy controls. Increases in DA release were not found. However, when compared with placebo 300mg of Caffeine increased the availability of D2/D3 receptors significantly in the ventral striatum and putamen, but not in caudate [7]. Caffeine-induced D2/D3 receptor increased availability in the ventral striatum did associate with caffeine-induced increases in alertness

at doses typically consumed by humans. The increases of availability of DA D2/D3 receptors found by Volkow, *et al.* [7] showed that caffeine does not increase DA in the human striatum and consequently decrease D2/D3 receptor availability. Instead, these surprising findings reflect an increase in D2/D3 receptor levels in the striatum or changes in affinity with caffeine and alertness suggesting that chronic caffeine might enhance arousal, in part, by upregulating D2/D3 receptors without releasing DA.

We propose herein that the action of Caffeine to increase D2/D3 receptor availability could have benefit for both the recovery community and health subjects seeking well-being/happiness (open happiness as suggested by Coco Cola slogan) especially in the face of societal stress. So, through its interaction with A2AR Caffeine may block DA release, we are speculating that chronic effects of caffeine may potentially increase DRD2 receptors overcoming the high genetic risk of carrying DRD2 A1 allele with a reduced number of D2 receptors that lead to relapse especially with high stress [8]. Dobbs, *et al.* [9] found compelling evidence for a critical role of striatal D2Rs in shaping basal ganglia connectivity; even among neurons that do not express D2Rs. In response to the manipulation of striatal D2R levels, a circuit-wide restructuring of local and long-range inhibitory connectivity within the basal ganglia, accompanied by multiple alterations in dopamine-dependent behaviors, has been observed in animal models. These findings have clinically a complicated mechanism but through required research may lead to novel ways to overcome genetically induced hypodopaminergia or deficient DA function based on abnormal receptor density [2,8,9].

It is important to point out a neurochemical paradox related to potential Caffeine benefits in the recovery space. While it is true that chronic Caffeine increases the availability of D2/D3 receptors the paradox relates to the fact that this increased availability is at the expense of attenuated DA release at the Nucleus Accumbens. This fact by itself may have negative consequences in terms of the recovery community especially individuals born with high genetic risk linked to hypodopaminergia. So, while it is interesting in finding the chronic Caffeine-induced increased availability of D2/D3 receptors as observed by Volkow, *et al.* [7], it must be met with caution because of Caffeine's effect to block DA release. One laudable goal would be to find compounds or complex's that could not only up-regulate DA function but at the same time regulate neurogenetic insults of the brain reward circuitry to asymptotically approach normality.

While this paradoxical effect will be very critical for the recovering Reward Deficiency Syndrome (RDS) community, it may have direct unforeseen effects for the general population under normal stressful conditions seen every day whereby, epigenetic insults are impacting DA balance in the brain on neurotransmitter homeostasis processing [10].

Author Contribution

All authors contributed equally

Conflict of Interest

There are no conflicts of interest to report concerning the content of this article.

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