Caffeine and Substance Use Disorders

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CAFFEINE IS THE most consumed psychoactive drug in the world. As a psychostimulant, it shows all the pharmacological properties of classical psychostimulants, such as cocaine and amphetamine. Those properties include arousal, motor activation, and reinforcing effects. Nevertheless, those effects are milder for caffeine, which depends on its unique mechanism of action, adenosine receptor antagonism. Classical psychostimulants produce a direct potentiation of central dopaminergic, noradrenergic, and serotonergic neurotransmission, by acting on catecholamine and serotonin transporters. Caffeine, instead, indirectly activates those and several other ascending neurotransmitter systems (cholinergic, histaminergic, and orexinergic) by removing an inhibitory presynaptic adenosinergic tone, mediated by the effect of endogenous adenosine on adenosine A₁ receptors. Caffeine-induced modulation of the dopaminergic system also depends on postsynaptic mechanisms that depend on assemblies of adenosine and dopamine receptors (A₁-D₁ and A_{2A}-D₂ receptor heteromers) (for review see Ref. 1).

The same as for classical psychostimulants, the effects of caffeine on the dopaminergic system are largely responsible for its relatively mild motor activating and reinforcing effects.¹ However, it has been difficult to definitively show a psychostimulant-like biochemical profile of caffeine in the experimental animal. The hallmark of that profile is a significant increase in the striatal extracellular concentration of dopamine, and this has only been clearly seen in a distinct region of the ventral striatum.¹ In this issue, Ferré *et al.*² review recent results that indicate that paraxanthine, the main metabolite of caffeine in man, produces stronger motor activating effects and a more significant striatal dopamine-releasing effect than caffeine. This unique pharmacological profile of paraxanthine depends on an additional selective mechanism, other than adenosine receptor antagonism: inhibition of cGMP-preferring phosphodiesterases. These results open up the possibility that a part of the reinforcing effects of caffeine might depend on paraxanthine, which can reach significant plasma levels upon chronic caffeine intake.

The overwhelming caffeine consumption all over the world basically demonstrates its reinforcing effects. Several epidemiological studies indicate that regular caffeine intake creates dependence, which in part depends on withdrawal symptoms. But should we consider caffeine as a drug with potential abuse liability? Researchers and clinicians have been debating about the addictive potential and clinical importance of caffeine use. In this issue, Budney *et al.*³ present

the results of a survey among addiction professionals (members of six clinical/scientific organizations that focus on addiction) about the clinical importance of caffeine withdrawal and dependence. The survey indicates that most professionals believe that caffeine withdrawal and dependence exist and are clinically relevant. However, there was no consensus about the need of including both clinical diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM), with a main reason being a perception of less severity compared to withdrawal and dependence of the already included abused drugs. The Budney *et al.*³ survey was performed before the release of DSM-5, which includes caffeine and cannabis withdrawal as diagnoses. Important changes in DSM-5 as compared to DSM-4 are the merging of previous abuse and dependence criteria as criteria for a single disorder, now named "Substance Use Disorder" (SUD). Furthermore, craving has been added and legal problems have been removed as new and old criteria, respectively. The final 11-criteria list of the DSM-5 allows providing a score of severity, with 2–3, 4–5, or more than 5 as mild, moderate, and severe, respectively. According to these criteria, tobacco has been aligned with other substances, but not yet caffeine.

Apart from analyzing the potential clinical importance of caffeine by itself, another aspect that might deserve even more consideration is its interactions with other addictive substances. One fast-growing danger in adolescents and young adults is the combined intake of alcohol and caffeinated beverages (usually in the form of high-energy drinks). Mechanistically, caffeine antagonizes the unwanted effects of alcohol by blocking the A₁ receptors that mediate alcohol's somnogenic and ataxic effects.⁴ Furthermore, the A₁ receptor-mediated unwanted anxiogenic effects of caffeine may be ameliorated by alcohol-induced increases in the extracellular concentration of adenosine.⁴ Moreover, by means of interactions between A_{2A} and D₂ receptors, caffeine-mediated blockade of A_{2A} receptors can potentiate the effects of alcohol-induced dopamine release, including its reinforcing effects.⁴ Mixing alcohol and caffeine has been found to be significantly associated with high-risk drinking behaviors and adverse alcohol-related consequences among college students. In the present issue, O'Brien *et al.*⁵ analyze the role of personality, in particular, the sensation-seeking trait, in the characteristics and consequences of caffeine-alcohol drinking. The study shows that among college students, sensation seeking moderates the risk of alcohol-associated injuries requiring medical attention. More epidemiological studies will

undoubtedly confirm the dangers of this popular combination. Even though alcohol is already considered as a substance of abuse, and even though we can question the addictive properties of caffeine, intake of the caffeine-alcohol combination might have to be considered as a SUD on its own.

Another popular combination used by young adults is caffeine (often as high-energy drinks) with amphetamine-related drugs, such as methamphetamine and MDMA (ecstasy). Furthermore, unintentional combined consumption of caffeine and amphetamine-related drugs is very common, since caffeine is often present as an additive. There is clear experimental evidence indicating that caffeine does not potentiate only the psychostimulant effects of amphetamine-related drugs. This is quite predictable when considering the combination of mechanisms of action mentioned above, particularly the direct and indirect effects on dopaminergic neurotransmission. However, as reviewed by Frau *et al.*⁶ in this issue, there is strong experimental evidence, which also indicates that caffeine potentiates the acute toxic effects of amphetamine-related drugs, such as seizures, hyperthermia, and tachycardia. The relevance of these interactions remains to be determined, but it should be alarming in view of the popularity of these drug associations and the fact that those toxic effects are an important determinant of the fatalities associated with amphetamine-related drug intake.

Finally, a less explored, but potentially significant combination is caffeine and marijuana. In this issue, Sousa *et al.*⁷ review recent experimental findings that indicate the existence of functionally significant interactions between the adenosine and cannabinoid systems. These interactions seem to be particularly important in the hippocampus, where A₁ and cannabinoid CB₁ receptors are colocalized and are involved in mnemonic and cognitive processes. Antagonistic interactions between these receptors underlie a caffeine-induced potentiation of cognitive impairment caused by THC. The reviewed interactions are relevant enough to justify the performance of epidemiological studies that could disclose the existence of particularly deleterious cognitive effects associated with the combined intake of caffeine and marijuana.

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