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Research Article

Caffeine Is A Stimulant But It May Not Be A Psychostimulant

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Caffeine is a stimulant!

Caffeine is undoubtedly a "stimulant" but it is likely not a psychostimulant because clinical literature has never shown caffeine to directly produce psychosis in humans. There is such a phenomenon as ''stimulant psychosis,'' but according to published medical literature and, more importantly, the Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition (DSM-V), [1] there does not appear to be any evidence that caffeine is causative in psychoses. In fact, caffeine is not listed in the DSM-V as a substance abuse disorder as it was removed from the Substance Misuse Category of DSM-V. This provides further evidence that caffeine is not a psychostimulant due to the well-established fact that psychosis is comorbid with substance abuse [2]. Indeed, a partial quote from DSM-V follows herein:

Substance use disorder in DSM-5 combines the DSM-IV categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe. Each specific substance (other than caffeine, which cannot be diagnosed as a substance use disorder) is addressed as a separate use disorder (e.g., alcohol use disorder, stimulant use disorder, etc.), but nearly all substances are diagnosed based on the same overarching criteria. In this overarching disorder, the criteria have not only been combined, but strengthened.

Thus, caffeine, a purine alkaloid, is not one of the stimulants that enables a psychotic condition to actually occur in human or murine subjects that are using or being administered ''non-excessive'' amounts of this substance.

Even though this often-debated molecule called caffeine has not been empirically or clinically proven to cause psychosis, a few rare cases will be pointed out, *a priori.* These are isolated episodes in which a caffeine psychosis may or may not have occurred. For example, there was one incidence of caffeine psychosis published in the New England Journal of Medicine in October 1936 [3]. In this article, the authors reported a case of caffeine psychosis produced by high doses of caffeine, and the effects were described as mental confusion and gastrointestinal diarrhea. The authors further describe caffeine intoxication with high-dose intravenous caffeine administration that caused psychosis depicted as "toxic" and characterized by "final weakness,'' ''irregularity of the cardiovascular system,'' ''slight increase in blood pressure,'' and ''slight blood vessel dilation.'' Furthermore, the authors describe the human subject who has just been intravenously injected with caffeine as having ''clearer ideas'' and ''more flowing thought process'' as their fatigue disappears. In contrast smaller doses of caffeine were not described as toxic and, instead, gave the subject ''absolute strength'' with ''peripheral muscle irritability".

Another paper reports that caffeine taken at high doses is contraindicated in previously diagnosed psychotic patients; this further delineates the important interaction between substance abuse and psychosis while supplementing previous research that critically highlights the toxicity of high doses of caffeine [4]. As reported, this was a case of ''apparent chronic caffeine psychosis'' characterized by delusion and paranoia after high caffeine intake. The subject's symptoms resolved 7 weeks after caffeine intake was lowered, while antipsychotic medication was not medically judged as needed. An article from one other laboratory reports that long-term caffeine use can lead to mild physical dependence, but withdrawal symptoms are unremarkable and do not persist beyond 4 days. Indeed, neither caffeine

use nor a pathological or compulsive form of its use has ever been documented [5]. Thus, the general consensus is that caffeine is not psychoactive and, therefore, does not appear to be a psychostimulant or a substance of abuse as stated in DSM V. The conclusion is clear: the rare exception of toxic symptoms, derived from the caffeine molecule, lies in its excessive and high intake usage.

Caffeine acts at adenosine receptors: Both adenosine and caffeine molecules are comprised of a purine. However, the purine in the adenosine molecule is a nucleotide attached to a ribose sugar. Due to this unique structure, the adenosine molecule spins away from the caffeine molecule, enabling a differential molecular structural activity. Adenosine is ubiquitous in every human cell, and it gives us a tremendous amount of energy through its monophosphate and triphosphate homeostatic derivatives. Adenosine is known as an inhibitory neurotransmitter, and it may play a crucial role in neuromodulation via the hypo-function hypothesis of psychosis [6].

The Adenosine Hypofunction Hypothesis of Psychosis

In fact, there is an adenosine hypothesis of psychosis [7]. In this hypothesis, adenosine is not described as a psychotic. Rather, the discussion centers around hypofunction of adenosine, as well as its interaction with other molecules such as glutamate and N-methyl-D-aspartate, as these molecules are known to be involved in psychotic processes. Also included in this more recent hypothesis are the biogenic amine neurotransmitters such as dopamine and serotonin. The adenosinergic hypothesis states that the biogenic amine hypothesis of schizophrenia by Schldkraut and Kety, as reviewed by Meltzer and Stahl [8], may not fully answer strategies for the pharmacotherapy of the negative versus the positive symptoms of psychotic behavior from schizophrenia. This recent hypothesis reports that adenosine is a homeostatic, bioenergetics network acting as modulator that is able to affect complex circuits synergistically and at different levels of receptor-dependent pathways including epigenetics. In this hypothesis of adenosinergic hypofunction, dopamine and glutamate neurotransmitters interact with the adenosine molecule to promise much-needed treatment for negative and positive psychotic polarity.

On the other hand, Brown and Short [7] discuss adenosine as a neuromodulator that plays a role in reward-related behavior both as an independent mediator and by way of adenosine receptor interactions with other receptors as adenosine levels are elevated upon exposure to drugs of abuse. These authors continue to specify A (2A) receptors as adenosine receptors that are ''ideally suited to influence the signaling of neurotransmitters relevant to neuronal responses and neuroplasticity that underlies the development of drug-taking and drug-seeking behavior.'' The rationale for suggesting that A (2A) receptors are excellent targets for treatment of adenosine-induced psychosis from drug abuse is based on findings that show that A (2A) receptors reside in receptor ''clusters'' with dopamine and glutamate receptors in neuroanatomical regions of brain that are known to be directly related to brain reward and reinforcement behavior. The important caveat in this discussion is that reinforcement, addiction and psychosis are not the same phenomena.

Psychosis

Let us consider the condition of psychosis in order to realize the consequent detriment to the field of caffeine science when categorizing this caffeine nutrient molecule as a psychostimulant in such a laissez-faire manner. In one view of psychosis, cognitive processes in the cerebral areas of attention and perception are involved [9], whereas the previous definition of psychosis was explained as a breakdown of the ego [10]. Psychosis is currently recognized as cognitive disorganization [11,12], and one might simply say that psychosis is sensory affect that is undergoing overload. For example, a patient, suffering from psychosis may remark, ''too many things are coming into my mind,'' ''the thoughts feel bigger,'' ''the person I am talking to looks bigger.'' Therefore, one's ability to keep sensory information organized in channels is imperative for control of central nervous system functioning.

Brain Reward, Pleasure Centers, Reinforcement

Panel C of Figure 1 shows a schematic of neuronal circuits in the brain. Generally speaking, the pons is of significance here for two reasons. First, both the pons and its nuclei channel sensory affect; and second, because somatodendrites, cell bodies for synthesizing biogenic amines such as dopamine, are in close proximity to the pons. Also in close proximity to the pons are neuronal terminals such as the nucleus accumbens that instigate - along with the hypothalamus, the septum, the reticulum, and the reticular activating system - a myriad of brain reward mechanisms such as the neurological effects of reinforcement and pleasure that modulate behavior. There is some debate as to whether these pleasure centers are stimulated by motivation of pleasure and not the pleasure itself. Nonethe-

less, abundant evidence suggests that human and murine pleasure/reward/reinforcement happens across a distributed brain circuit in which the sub-cortexes, as well as cortical regions, are involved.

According to Dr. James Olds at McGill University, the brain reward hypothesis involves stimulation of specific central nervous system pathways for neurotransmitters and neuromodulators to connect and interact to make one ''feel good''. Olds *et al.* electrically stimulated specific neuroanatomic substrates in the brain *in vivo*. Mammalian responses to this neuronal trigger of stimulation demonstrated that pleasure/reward/reinforcement was experienced; the pleasure was reflected in remarkable positive behavioral reactions to the stimuli [13,14]. This pleasure/brain reward/reinforcement hypothesis has reached consensus worldwide. The hypothesis of brain reward by Dr. Olds has been empirically, continually, and strongly supported by notable pioneers in the brain reward field [15] and those advancing the field by using molecular heteromer technologies [16] and neuromolecular nanobiotechnologies [17].

Now, let us look at the molecular structures to see the differences between drugs that cause psychosis and those that do not.

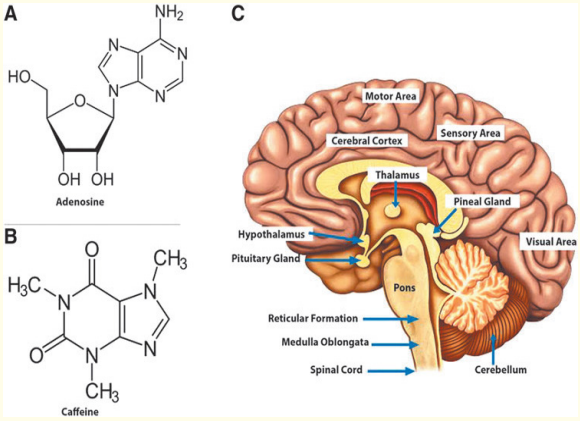

Figure 1: *(A) The adenosine molecule. Note that this purine nucleotide is comprised of an adenine base which is bonded to the ribose sugar (see the molecular structure on the left side of the molecule); the connection is between the nitrogen on the adenine base and the double bonded oxygen on the first carbon of the ribose sugar. (B) The caffeine molecule, a purine alkaloid, is depicted. Caffeine is known as a nutrient substance, a food source. (C) Schematic depiction of the mesocorticolimbic neuronal circuitry and related neuroanatomic substrates involved in brain reward/reinforcement mechanisms , as well as in the neuropathology of addiction.*

These studies may have placed caffeine (Figure 1B) and adenosine (Figure 1A) in the realm of brain reward because mesocorticolimbic neuronal dopaminergic circuitry in somatodendrites, ventral tegmentum nerve terminals, and nucleus accumbens, as well as associated areas such as amygdala, hippocampal somatodendrites, and locus coeruleus, are likely influenced by caffeine in the context of adenosine and/or adenosine receptors. Channeling sensory auditory signaling through the pons nuclei via the cochlear nucleus is affected by caffeine and adenosine [18]. Indeed, caffeine and adenosine can be reinforcers, but the road from reinforcement to addiction is winding with elusive complexities since there are higher pleasures directly related to the brain's default neuronal circuits in addition to the neuronal sensory circuitry of reward. These circuits existentially enable faculties that the non-prescient mammalian brain cannot likely fathom. These are, for example, cognition and a life of meaning and happiness. The hedonic brain is the unhappy brain, the brain that cannot feel pleasure; it is the brain that fast forwards chronic neuropathologies, affective disorders such as depression and addiction, and unyielding pain both peripherally and centrally.

A Most Notable Difference in the Molecular Structure of Adenosine versus Caffeine

Adenosine is a purine nucleotide comprised of an adenine base bonded with a ribose sugar nucleotide, thus making the molecular structure of adenosine, a nucleoside. The adenine base in adenosine is bonded to the ribose sugar; the connection is between the nitrogen on the adenine base and the double-bonded oxygen on the first carbon of the ribose sugar by an intermolecular dehydration. It is the oxygen bonded to the second carbon of the ribose sugar that distinguishes between the ribose in Ribose Nucleic Acid, also known as Ribonucleic acid (RNA), and the deoxyribose in Deoxyribose Nucleic Acid, also known as Deoxyribosenucleic acid (DNA). However, it is not the purpose of this paper to discuss whether or not a tropane, tropine or tropane-like molecular structure is related to the molecular structure of adenosine.

The author studied the differences in the distinctive properties of these nitrogenous compounds, the alkaloids, and through the literature and experimentally derived data, was led to believe that the study of these differences may shed some light on the reinforcement path to addiction. It is simply suggested that the molecular structure differences between caffeine and cocaine, especially the cocaine tropane alkaloid, further elucidates the tropane ring as a possible key to open a door revealing the intricacies of reinforcement mechanisms versus neuropathological mechanisms of addiction in the context of psychosis. Indeed, there are known dual diagnostic therapies for psychosis and addiction. This interrogative perspective, written to enlighten and appreciate some degrees of reward experienced in our daily lives, addresses only the cocaine tropane alkaloid as having such dual properties of psychosis and addiction whether or not these present in the patient separately or combined.

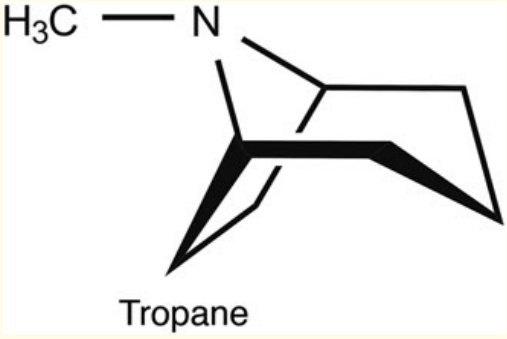

Figure 2: *The tropane ring, a fascinating, naturally occurring bicyclic chemical ring system that lends it to many pharmaceutical and therapeutic applications. The role of the tropane skeleton in drug research has been pioneered by Laszlo Gyermek, MD, PhD. Professor of Anesthesiology (Ret). University of California at Los Angeles, Harbour UCLA Campus, and Los Angeles Biomedical Research Institute, Torrance, CA. The bicyclic ring system of tropane can be construed as a condensation product of a piperidine and pyrrolidine ring with a shared N atom. Thus, the exact chemical name of tropane is: 8 Methyl aza bicycle (3.2.1) octane. This name also characterizes the branching of this bicyclic ring system, which has distinct pharmacological significance. See http://inhn.org/fileadmin/archives_new/Gyermek/Gyermek_TheRole OfTropaneSkeleton.pdf*

Cocaine Is a Psychostimulant and Is Known to Cause Psychosis

In fact, reports of cocaine-induced psychotic patients are happening at an alarming rate. The first cases were reported in abundance in the 1990s, and presently, there is still no scarcity of clinical cases of cocaine-induced psychosis [19-29]. Cocaine-induced psychosis is so prevalent that it has its own abbreviation, CIP [28]. In the Medscape report [29], the authors use the DSM-IV-TR to describe ten more cases of CIP.

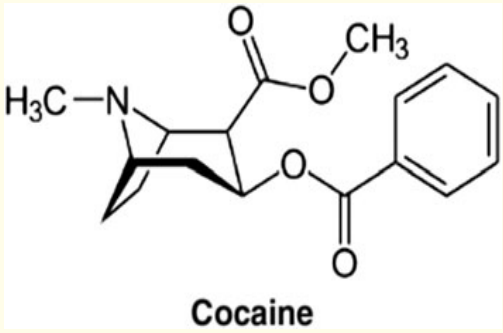

Figure 3: *The cocaine molecule. Note the tropane ring in bold. Cocaine is a Schedule II drug listed in the Federal and New York State Drug Enforcement Agency Codes.*

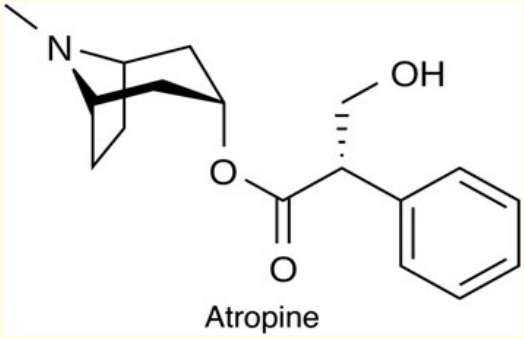

Figure 4: *The atropine molecule. Note the tropane ring in bold. Atropine, although not a schedule II drug listed in the Federal and New York State Drug Enforcement Agency Codes, is reported to be a ''possibly addicting drug.'' Atropine addiction occurs especially if it is used with another drug that has inherent addicting properties.*

A thorough history pertaining to the type of symptoms experienced by the patient and the timing of these symptoms in association with cocaine abuse is necessary to make each diagnosis. Other cocaine-induced medical problems may be present and/or coexistent with any of these ten cocaine-induced psychiatric conditions. For example, a patient may present with specific clinical criteria that led to the diagnosis of a cocaine-induced psychotic disorder with hallucinations. That same patient also may report chest pain, a symptom that could be associated with cocaine-induced acute coronary syndrome, pneumothorax, or pulmonary edema. The report continues on to cite CIP dysfunctions as intoxication, withdrawal, intoxication delirium, CIP with delirium, CIP with hallucinations, CIP mood disorder, CIP anxiety disorder, CIP sexual dysfunction and CIP sleep disorder.

The broad category of cocaine related disorders can be subdivided into cocaine use and cocaine disorders such as delusions (hanging on to beliefs that are clearly nonexistent) and hallucinations (hearing and seeing things) [30]. A clinical case of cocaine psychosis presenting with hallucinations and delusions is reported [31]. This article describes a patient in the emergency department who had binged on crack cocaine. The patient heard ''voices in his head who were telling him to kill himself and the patient continued to believe there was a plot against him.'' These auditory hallucinations have been given the definition ''strange perception of sounds" [32].

Cocaine Causes Stimulant Psychosis

Stimulant psychosis is a psychotic disorder that occurs in some people who use stimulant drugs. Stimulant psychosis commonly occurs in people who abuse stimulants, but it also occurs in some patients taking therapeutic doses of stimulant drugs under medical supervision [33]. The most common causative agents are substituted amphetamines and cocaine [34].

Cocaine Is a Tropane Alkaloid

Cocaine is a tropane alkaloid as it has a tropane ring in its molecular structure. The structural activity between cocaine and caffeine molecules is dramatically different. It is true that cocaine and caffeine are alkaloids, but cocaine is a tropane alkaloid and caffeine is a purine alkaloid. Both alkaloids are molecular compounds derived from nitrogenous metabolism in plants, and it is true that both molecules are reinforcing as they are described as bringing about a *joie de vivre*. However, cocaine is a psychostimulant. Caffeine, in contrast, may not be a psychostimulant albeit it has been a known stimulant throughout the ages. To repeat, psychosis and addiction are not the same; in the next section, only addiction and the cocaine alkaloid are discussed.

Addiction and the Cocaine Alkaloid

In the science of pharmacology, cocaine is listed in a class of drugs called ''local anaesthetics.'' Most interestingly, cocaine is the only drug in this class of anaesthetics that has a chemical formula comprised of a tropane ring and is, moreover, the only one that has been shown to cause addiction. Thus, the correlation between tropane and addiction may be, as pointed out before, a simple key to unveiling the complexities of addiction. Indeed, empirical studies have reported that molecules with the tropane ring are primarily the ones that show the ability to cause what we might call addiction again, given the caveat that the neuropathology of addiction remains to be solved. The suggestion in the literature, though, is that the tropane ring may well be the addicting part of any molecule, and this fact, then, can lead us to insightfulness in each intricate step that brings one from hedonia/reinforcement/pleasure/reward to an addiction/anhedonia/a neuropathological state.

Cocaine and Atropine

Cocaine is an ester of benzoic acid and methyl ecgonine; ecgonine is a base, an amino acid alcohol closely related to tropine, the amino alcohol of atropine. Atropine is sometimes called ''possibly addicting.'' This is a surprising concept in the conventional sense of pharmacology. One would not expect atropine, a belladonna alkaloid, to possess addicting properties because it is an important physiologic anticholinergic in the autonomic nervous system, and it is not generally reported as psychogenic. Atropine is possibly addicting [35,36] because the atropine molecule has a molecular structure that is comprised of the tropane ring. The similarity in the chemical formulas in atropine and cocaine molecules again emphasizes the critical role of the tropane ring in the neuropathology of addiction. Molecular structures for cocaine and atropine are shown in Figures 3 and 4 and have been previously described with data from this laboratory [43].

Then, to emphasize the role of cocaine as a local anaesthetic that is addicting, cocaine does have the same fundamental structure as the other classical synthetic local anaesthetics, but the dramatic difference in the molecular structure of cocaine versus all other local anaesthetics lies in the cocaine tropane ring. Indeed, it may be true that the tropane ring may be the source of cocaine's ability to lead the path from controlled reinforcement and enjoyment to the unfortunate maladies associated with addiction pathology. It is important to note that each molecular structure of each of the other local anaesthetics are not comprised of the tropane ring and are, correspondingly, not known to be addicting.

Finally, it is the dopamine transporter studies that have published the critical nature of the tropane ring in addiction [36-38]. The dopamine transporter is believed to be involved in the mechanism by which dopamine remains in the synapse. The work of scientists in the field of molecular pharmacology has experimentally shown the correlations amongst cocaine, tropane, and addiction [37,38].

Conclusion

Caffeine is a stimulant as it produces reinforcement/brain reward. However, given the caveat that all stimulants may not produce psychoses per se, caffeine may not be a psychostimulant because it is not psychoactive. The molecular structure of caffeine is not comprised of a tropane ring as it is a purine alkaloid. Caffeine blocks cocaine-induced dysfunctional neurochemistry and behavior via adenosine receptor antagonists; the responses are based on sex differences [39]. Caffeine has also been shown to restore to normal estrus cycle changes induced by cocaine [40]. Caffeine is reported to be medically beneficial in the treatment of Parkinson's disease [41].

Adenosine and adenosinergic receptor interactions and derivatives may have reinforcement effects but these are not in a category as such. Adenosine is a purine alkaloid, comprised of an adenine base and ribose sugar; its molecular structure is dramatically different from that of caffeine. Caffeine/adenosine agonist and antagonist interactions are well known. Adenosine is medically beneficial in many instances, for example in cardiovascular disease as a vasodilator [42].

Cocaine is a psychostimulant; it is psychoactive because it has been shown to be causative in psychosis. Cocaine is a tropane alkaloid. Cocaine produces reinforcement/brain reward, and it has been shown to do so to the extreme as it is causative in addiction neuropathology. Cocaine disrupts the sensory processing in the auditory neuronal pathway through the cochlear nucleus, and the effects are sex differentiated [43]. Cocaine has been a controlled substance under the United States Federal Drug Enforcement Code since 1970. Cocaine is medically beneficial in pharmacology as a local anaesthetic and is prescribed only in limited cases [36].

Atropine is a tropane alkaloid, and it is a belladonna alkaloid; it dilates the pupils and is anecdotally referred to as the ''beautiful woman'' alkaloid. Atropine is possibly addicting likely due to its tropane molecular structure. Atropine has a wide spectrum of use clinically ranging from influencing gastrointestinal tract function to use in ophthalmic preparation by paralyzing the iris sphincter to cause cycloplegia, a necessary paralysis used successfully in everyday cataract eye surgeries [36].

In closing, then, it is submitted that caffeine may not be a psychostimulant and may not be causative in psychosis. Thus, clinical psychogenesis reports can be relied on to decipher stimulant psychosis. Furthermore, an in-depth study of molecular structures of stimulants and other reinforcers will provide strategic discoveries in the drug addiction field. Clues from stimulant molecular structures can and will assist in the analyses of unique mechanisms and subsequent pharmacotherapeutics. Finally, addiction neuropathology requires greater in-depth studies than are discussed herein.

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