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The Relationship between Psychoactive Drugs, the Brain and Psychosis

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Abstract

This paper explores the interaction between four psychoactive drugs, namely MDMA (Ecstasy), Cocaine, Methamphetamine and LSD, with neurotransmitters in the brain with the aim of understanding what links exist between these drugs and Psychosis. The paper is restricted to three neurotransmitters – dopamine, serotonin, and norepinephrine (noradrenaline) and explores in some detail how they are affected by the aforementioned drugs. The paper aims to go beyond existing research on drugs and psychosis which has been primarily limited to cannabis (Marijuana) and psychosis. The findings and conclusions drawn show that all the drugs explored have the potential to induce psychosis in abusers to some degree; the effects vary from drug to drug.

Introduction

Drug use is a topic of interest for a variety of reasons. The distribution and consumption of illegal substances is a problem in many parts of the world today. Demand for such substances is present because of the effects that they have on the human mind and body those abusers of drugs desire. However, no user desires the negative effects that drugs have on one's mind and body. One of these negative effects is psychosis [1-3]. In this paper we looked at the relatiosnship between Psychosis and Drugs. There are different categories of drugs, such as depressants, stimulants, narcotics and psychedelics. This paper focuses primarily on psychedelics. These are chemical substances that affect the central nervous system, affecting brain function. Because of the way psychoactive drugs affect brain function, there are changes in perception, mood, consciousness, cognition and behavior [4,5].

While certain drugs like Marijuana have been used for medical purposes to treat both physical and psychological disorders, such application is limited and the use has been questioned [6]. Also the quantity of substances entering a person's body for medicinal use is relatively low. For recreational use, higher amounts have to be ingested to bring about the changes that result in hallucinations and other unusual behavior. Long term recreational use, in large amounts, has detrimental effects on the mind as well as the body.

All drugs affect the neurotransmitters in the brain. Different drugs affect different neurotransmitters, and therefore have different effects on the human body. Some drugs mimic neurotransmitters, e.g. synthetic opioids act on the opioid receptors in periaqueductal grey of the midbrain [7] whereas some alter neurotransmission by interacting with molecular components of the sending and receiving process, an example being cocaine. Some drugs alter neurotransmission in different fashion. Benzodiazepines enhance the response of receiving cells mediated by serotonin, possibly with the involvement of GABA [8]. One of the unwanted effects of many of the psychoactive drugs is psychotic symptoms. However, most research has been centered on cannabis (Marijuana) use and Psychosis. This paper therefore explores to what extent other psychoactive drugs affect psychotic symptoms and illnesses.

In order to delve into the above topic, secondary research from multiple sources, case studies, as well as testimonials from users about their perspective on the issue was used. This paper is limited in scope to psychoactive drugs only. The drugs explored in this paper are: MDMA, Cocaine, Methamphetamine and LSD.

A major limitation in the writing of this paper is that no primary research could be conducted and certain secondary research used is greater than ten years old. In addition, not all psychoactive drugs have been explored.

Drugs, Neurotransmitters and the Brain

Drug use in one form or another has been present all over the world. While use of more 'traditional' drugs such as cocaine, heroin and marijuana have not seen an increase, synthetic drugs are becoming more popular and their use has increased substantially, especially in Asia and developing regions in Africa and 27 million people or 0.6% of the world's population are problem drug users [9]. These drugs are popular because of the effects they produce and the speed with which they produce it. Many drug users are not aware of the lesser known negative effects that drugs have, such as psychosis and psychotic symptoms. All psychoactive drugs, synthetic or natural, affect the brain by interacting with receptors of neurotransmitters that are present in the brain. But a question that commonly comes up is, if the substance use, especially methamphetamine, cannabis, alcohol and tobacco are due to an underlying vulnerability in patients and cause both substance use and a psychotic disorder.

Dopamine systems play important roles in motivation, arousal, cognition and reward and its release has a stimulating effect. It is responsible for cognitive alertness [10]. Drugs can increase or decrease dopamine release resulting in varied effects. Serotonin plays important roles in the regulation of moods, learning, appetite and

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sleep. Alterations in serotonin levels affect mood [5]. Norepinephrine or noradrenaline, like dopamine, has a stimulating effect and plays a role in learning. It is most responsible for vigilant concentration. It also plays a part in stimulation the heart, blood vessels and sweat glands among other parts.

Drugs and Psychosis

Drugs such as MDMA, Cocaine, etc. produce certain effects, such as hallucinations and delusions [11]. These are used primarily to obtain the excitatory actions on brain reward systems. Paradoxically, excessive drug intake can decrease the activity of reward systems [12].

MDMA and methamphetamine

MDMA or (±) 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") is a popular recreational drug that selectively damages brain serotonin (5-HT) neurons in animals at doses that closely approach those used by humans. It is most commonly consumed orally in the form of pills. The drug affects three neurotransmitters in the brain: serotonin, dopamine, and norepinephrine (or noradrenaline). When the drug enters the brain, it leads to these neurotransmitters being released from their synaptic vesicles in neurons. This results in increased neurotransmitter activity. MDMA causes substantially increased serotonin release and dopamine release to a lesser extent [13]. The excess release of serotonin causes the mood elevating effects that MDMA user's experience. However, by releasing large amounts of serotonin, MDMA causes the brain to become significantly depleted, contributing to the negative behavioral after effects that users often experience for several days after taking MDMA. Also, MDMA can damage serotonin containing neurons, and MDMA users showed decreased global and regional brain 5-HT transporter binding compared with controls. [13,14] Methamphetamine, commonly known as 'Crystal Meth' or 'Ice', is a stimulant drug with strong effects on the user. The drug boosts energy levels and produces an intense 'high' for the user. It is commonly swallowed, snorted, smoked and sometimes injected, depending on the user and the cut of the methamphetamine. The high produced by methamphetamine lasts for a long duration, sometimes up to 12 hours. Like cocaine, methamphetamine affects reward centers in the brain as well as centers that control memory. When the reward centers are stimulated there is a massive release of dopamine and the user experiences pleasure and extreme euphoria. Long periods of time (thirty to ninety days) can pass after the last intake of the drug before a user realizes that he is in withdrawal. Effects of withdrawal include craving, depression and loss of energy, anhedonia and suicidal thoughts. Long standing use causes reduced cortical gray matter [15] and frontal ventricular enlargement, hippocampal and cingulate gray matter loss [16]. Common withdrawal symptoms in users include craving, anxiety, depression, delusions, hallucinations, fatigue, panic attacks, and irritability.

Cocaine

Cocaine is a popular stimulant drug that is obtained from the leaves of the *coca* plant. It is commonly self-administered by snorting it in powder form or smoking it in the form of 'crack' cocaine. Smoking cocaine makes a crackling sound, hence the name. Cocaine, blocks uptake by neuronal plasma membrane transporters for dopamine, serotonin and norepinephrine, and its reward/reinforcement has been linked to actions on dopamine or to blockade of serotonin [17]. The substantially higher amounts of dopamine remaining in the synapses between neurons which causes the 'high' that a user of the drug feels. Dopamine plays a major role in the reward system of the human brain [10]. Therefore, higher dopamine levels lead to more pleasure and higher levels of confidence. Cocaine addicts show strong withdrawal symptoms including craving, depression, fatigue, irritability, agitation, and suicidal thoughts. Some of these symptoms can last for months following the cessation of heavy long-term use.

LSD

LSD (Lysergic acid diethylamide) is a well-known hallucinogen known by a myriad of street names. The drug was first synthesized in a laboratory in Switzerland in 1943 by a chemist by the name of Albert Hofmann. Contrary to most other drugs, there have been extensive laboratory studies on animals concerning the effects of LSD. LSD is normally orally ingested by licking small squares of blotter paper that have been soaked in the drug as well as in the form of tablets called 'microdots'. LSD primarily affects serotonin receptors (Bennett JP, 1975) [18] which sends signal to other parts of the brain that there is an excess of serotonin, and these parts then respond by decreasing serotonin production. This causes the 'trip' from the drug, which is characterized heightened appreciation of sensory stimuli [19] e.g. seeing colors more vividly, and many users have claimed that there is a "TV show in the head". Onset of psychological and behavioral effects occurs approximately within 30 minutes of oral administration and effects can last till up to 8 hours. One interesting feature of LSD is that there is a loss of the typical effects after repeated doses. After 200 micrograms per day of LSD, the effects of the drug are reduced or not detectable altogether on the third or fourth day. After a gap of three to four days, the same initial effects are felt by the same dose that the brain had tolerated. Tolerance develops and dissipates very quickly. Withdrawal symptoms for LSD use include anxiety, problems concentrating, problems with memory retrieval and cognition, depression, suicidal thoughts (if the drug has been used for an extended period of time and a high tolerance has been developed; it is a rare symptom to experience). Withdrawal effects from LSD do not last very long in most users.

There has been extensive research over the last twenty or so years revolving around substance related abuse and psychotic illnesses such as schizophrenia [20]. In common with Schizophrenia, misuse of some substances has been associated with brain structural abnormalities [21]. Recreational use of 'ecstasy' (MDMA) has become increasingly widespread. Review of empirical evidence concerning the persistent psychological sequelae of recreational use of ecstasy using open trial studies of recreational users have shown that presence or absence of persistent psychological problems are related to the extent of past exposure to ecstasy [22]. In 1991, two case reports concerning chronic paranoid psychosis and MDMA became popular in medical circles.

Case I

A 28 year old man was admitted after attempting to strangle his wife. He had been taking MDMA at weekends for 18 months. He had gradually increased his dose from two to 10 tablets a night and become suspicious that his wife was being unfaithful to him. He had checked on her movements, spied on her, and interrogated her and forced her to supply false confessions. Lately he had supplemented his intake of MDMA with occasional doses of cocaine. He had stopped taking any drugs six weeks before his admission. He had experienced a brief paranoid psychosis eight years earlier after misusing amphetamines. Also, his mother had suffered from schizophrenia.

Case II

A 22 year old man was admitted for assessment. Over the preceding two years he had consumed increasing quantities of MDMA with intermittent use of cocaine, lysergic acid diethylamide, and cannabis. Before admission he had been consuming three or four tablets of MDMA every night. He complained that his face had been gradually "pulled forward"; he avoided going out of doors, where he believed he was stared at and ridiculed. He had stopped misusing drugs (except cannabis) two weeks before admission. He had been adopted and had no knowledge of his biological family. He did not have a history of psychosis.

The above two case reports [23], along with other research [13,14] offer fairly strong evidence about the effects of MDMA on psychosis. The drug is a potent releaser of serotonin as previously mentioned. Thus, prolonged abuse of MDMA has been associated with psychotic symptoms such as flashbacks, anxiety, etc. However, Case II is not very conclusive due to the intermittent use of other drugs [23].

Cocaine induced psychosis is essentially stimulant psychosis caused by cocaine or crack abuse. The drug can cause certain psychotic

symptoms while a user is under its influence. These effects range from paranoia to delusional behavior to strong hallucinations.

Research on cocaine induced psychosis has been limited to a degree because diagnosing someone with cocaine induced psychosis is quite hard. Physical symptoms such as seizures and headaches or common in cocaine addicts, and they do not necessarily point to a psychosis. Hallucinations and delusions that cocaine induces are very similar to the hallucinations and delusions caused by schizophrenia, which is a psychotic illness.

Research conducted has shown that cocaine induced paranoia is common among chronic users of the drug [24]. In the study, 55 chronic cocaine users were interviewed by means of a standardized, semi structured interview. Of the 55 members of the study, 53% (29 members) reported experiencing transient cocaine induced psychosis. 28 of these 29 members experienced hallucinations. Those that experienced psychosis used significantly more cocaine in up to a year before the study than those who did not experience psychosis. The conclusion drawn from this study was that amount and duration of use of cocaine are linked to the development of psychotic symptoms in terms of severity of symptoms [24].

Methamphetamine is one of the most popular synthetic drugs, along with LSD. Demand and consumption of the drug have been growing in recent years, especially in the Asia Pacific region [25]. The drug rose to popularity in the 1990s in Asia, but had a strong following in Japan since the late 1940s. There were an estimated 550,000 methamphetamine users at this time, 55,000 of whom were said to have methamphetamine induced psychosis [26].

Symptoms of methamphetamine use that are also consistent with psychosis related symptoms include persecutory delusions and auditory and visual hallucinations. Methamphetamine associated psychosis is thought to be unique with its long duration of psychosis and recurrence without relapse of methamphetamine use [27].

Several Japanese studies have reported [28] methamphetamine associated psychosis was linked to long durations and more frequent use of methamphetamine. However, newer studies (in the US) indicate that psychotic symptoms can be induced even with short durations of use [27]. What is noteworthy here is that in the Japanese studies, users typically consumed only methamphetamine whereas the users in the studies conducted in the US used a mix of other drugs along with methamphetamine. There have been a number of cases of LSD induced psychosis in people who appeared to be healthy before taking the drug [29]. In most recorded cases, the psychosis-like symptoms are present for a short duration, but in certain other cases, they maybe chronic.

Research from the 1960s and 1970s lean towards the position, that LSD does not cause psychosis. Cohen (1960) estimated 0.8 per 1000 volunteers and 1.8 per 1000 psychiatric patients showed LSD induced prolonged psychosis lasting over 48 hours. Malleson [30] in later findings reported no cases of psychosis lasting more than 48 hours among his experimental subjects (170 volunteers) but estimated 9 per 1000 among psychiatric patients use some forms of the drug in the 1940s and 1950s [28].

But are psychotic symptoms caused by the psycho active substances, the only relation between these drugs and psychoses? Though increasingly questioned [31,32] the idea of association between substance misuse and schizophrenia as a means self medication for psychotic symptoms remain pervasive [33]. There are stuructural abnormalities in Schizophrenia and in those with substance use. A potential explanation between brain structural abnormalities and substance misuse is that, these abnormalities predispose to substance misuse and the cortical and hippocampal dysfuntions in schizophrenia are responsible for the greater reinforcing properties of the drugs in this population [34]. Long standing use of methampheamine causes reduced cortical gray matter [14] and frontal ventricular enlargement, hippocampal and cingulate gray matter loss [15].

Conclusion

To conclude the paper, this is a summarization of the findings:

Misuse and abuse of the drugs mentioned in this paper is associated with psychotic symptoms. The patients in both the MDMA case studies developed prolonged paranoid psychoses after prolonged drug usage. Also, given its capacity for neurotoxicity, MDMA can induce chronic psychosis *de novo* [21]. The results of research into Cocaine use reveal that amount of cocaine ingested and the duration of the addiction are linked to development of psychosis [23]. Research on methamphetamine and psychosis highlights that methamphetamine can induce psychosis even without very prolonged usage and there can be a recurrence of psychosis even after the drug has been stopped. There is insufficient data available on the relationship between LSD and psychosis. The position of researchers is that the occurrence of LSD induced psychosis is low, but the drug does have the potential to cause *de novo* psychosis.

Research in similar fields relates to genetic vulnerability to psychosis. Further research can be conducted to correlate drug use and its effects on latent psychosis as well as on those with a genetic vulnerability in an effort to understand the implications of drug use on mental health.

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