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What Can We Learn About Schizophrenia From Studying the Human Model, Drug-Induced Psychosis?

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When drug-induced psychoses were first identified in the mid-20th century, schizophrenia was considered a discrete disease with a likely genetic cause. Consequently, drug-induced psychoses were not considered central to understanding schizophrenia as they were thought to be phenocopies rather than examples of the illness secondary to a particular known cause. However, now that we know that schizophrenia is a clinical syndrome with multiple component causes, then it is clear that the drug-induced psychoses have much to teach us. This article shows how the major neuropharmacological theories of schizophrenia have their origins in studies of the effects of drugs of abuse. Research into the effects of LSD initiated the serotonergic model; amphetamines the dopamine hypothesis, PCP and ketamine the glutamatergic hypothesis, while most recently the effects of cannabis have provoked interest in the role of endocannabinoids in schizophrenia. None of these models account for the complete picture of schizophrenia; rather the various drug models mimic different aspects of the illness. Determining the different molecular effects of those drugs whose pharmacological effects do and do not mimic the various aspects of schizophrenia has much to teach us concerning the pathogenesis of the illness. © 2013 Wiley Periodicals, Inc.

Key words: psychosis; substances; schizophrenia; LSD; amphetamines

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INTRODUCTION

We are delighted to contribute to this special issue honoring Ming Tsuang, for two reasons. Firstly because we work at the Institute of Psychiatry in London, where the young Dr. Tsuang arrived in the 1960s to study the genetics of psychiatric disorder. He joined a number of (now) distinguished migrants to Eliot Slater's unit [Gottesman and Shields, 1971] including Irving Gottesman and Leonard Heston, and studied sib-pairs where both had psychiatric disorder; this work was rewarded with a PhD in 1965.

The second reason for our delight is not one of geography but rather of topic because Ming Tsuang has had a long interest in the role of drug abuse in schizophrenia [Tsuang et al., 1982]. Of course, when he arrived in London, he joined a unit where schizophrenia was considered a discrete disease with a likely genetic cause; Slater, for example, considered that there was a single dominant schizophrenia gene [Gottesman and Shields, 1971]. Consequently, psychoses due to other causes such as temporal lobe epilepsy, even if phenomenologically identical to schizophrenia, were considered as phenocopies rather than examples of the disorder secondary to a particular cause. A great deal of information has subsequently accumulated but the picture presenting in the clinic, as opposed to that seen in the experimental setting, has not been widely acknowledged as telling us much about schizophrenia itself. However, now schizophrenia is more appropriately viewed as at the extreme end of a continuum of psychosis where genetic and environmental risk factors combine to push the individual over a threshold into expressing the characteristic clinical syndrome [Stilo and Murray, 2010; Van Os et al., 2010]. It is time, therefore, to re-appraise the drug-induced psychoses, and how they can help us to understand schizophrenia.

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LSD and the Role of Serotoninergic Abnormalities in Schizophrenia

Albert Hoffman synthesized Lysergic Acid Diethylamide (LSD) in 1938, although he did not appreciate its hallucinogenic properties till 5 years later when he accidentally spilt the substance on his skin, and saw streams of "fantastic pictures, extraordinary shapes with intense kaleidoscopic play of colors" [Hoffman, 1980; Hoffman et al., 2005]. Later, he felt his body was possessed by a demon and his neighbor was a witch. Subsequent studies confirmed that administration of LSD can produce an acute psychosis, an effect which provoked considerable interest among psychiatrists. For example, Osmond and Smythies [1952] suggested that drugs such as LSD provided a model of psychosis with clues to what they called "the metabolic basis of schizophrenia."

Research into LSD took curious turns. The CIA began to investigate LSD as a "truth drug," and two researchers, together with the director of the Zoo in Oklahoma City, injected an elephant named Tusko with LSD to find out whether it would trigger madness in the animal. Sadly, 5 min later Tusko collapsed and died. Fortunately for elephants, they have not been subjected to further experiments with psychomimetic drugs. Some psychiatrists such as Osmond, who coined the term psychedelic, began advocating the therapeutic use of LSD, initially in their patients, and then more widely. By the 1960s, LSD had become a popular recreational drug.

Neuropharmacologists began to speculate that schizophrenia might be caused by the endogenous production of hallucinogens, such as dimethyltryptamine (DMT) [Rodriguez, 2007]. Szara [1956] had given DMT to healthy volunteers and reported hallucinations, distortions of perception and body image, speech disturbances, and euphoria. Differences in levels of DMT in urine and blood between schizophrenic patients and controls were reported [Franzen and Gross, 1965; Narasimhachari et al., 1972; Gillin et al., 1976]; for example, one of us (RMM) reported a greater DMT excretion in the urine of cases of schizophrenia compared to controls [Murray et al., 1979]; the reasons for these differences have never been established [Strassman, 1991].

Shaw and Woolley [1956] hypothesized that LSD might act on 5-HT-receptors, and Anden et al. [1968] suggested a direct agonist effect at 5-HT receptors. Glennon et al. [1983] proposed the 5-HT2 receptor subtype as the specific target of hallucinogenic drugs, and animal and human studies confirmed that the 5-HT2A-receptor mediated psychomimetic effects [Volleinweider et al., 1998]. The serotonin hypothesis of schizophrenia developed and received further support from the finding of 5-HT2-receptor abnormalities in post-mortem schizophrenic brains [Mita et al., 1986]; though in vivo studies of 5-HT2-receptor abnormalities reported conflicting results. Rasmussen et al. [2010] assessed 30 antipsychotic-naïve schizophrenic patients and matched healthy controls, finding that the patients had lower serotonin2A binding in the frontal cortex. Positron emission tomography (PET) scanning in humans showed that hallucinogens as psilocybin produced a marked activation of the prefrontal cortex caused by serotonergic [Arora and Meltzer, 1991; Joyce et al., 1993; Volleinweider et al., 1997]. The evidence that clozapine is particularly efficacious in treatment resistant schizophrenia provoked further interest because of the 5-HT2 receptor antagonism induced by this and other atypical antipsychotics [Lieberman et al., 1998; Meltzer, 1999; Tamminga and Holcomb, 2005].

Breakey et al. [1974] investigated the relationship between use of LSD and the age of onset of schizophrenia, and commented "On the basis of these results it seems plausible to conclude that the taking of drugs might play some precipitating role in the onset of schizophrenia, bringing this disorder on more quickly." This statement has been amply confirmed. Vardy and Kay [1983] suggested that LSD psychosis was a drug-induced schizophreniform reaction; moreover they concluded that there was a greater psychotic response to LSD in persons with genetic predisposition to schizophrenia.

Amphetamines and the Dopamine Hypothesis

However, LSD produces a psychosis with more visual and fewer auditory aberrations than is typical of schizophrenia, and gradually interest switched to amphetamines. The similarity of amphetamine psychosis to schizophrenia had been described in Japan by Tatetsu et al. [1956] and was confirmed in Britain by Connell [1958]. Subsequently, Angrist et al. [1974] found that amphetamine administered experimentally produced a paranoid psychosis in healthy individuals and exacerbated psychotic symptoms in one-third of patients with schizophrenia [Lieberman et al., 1987]; moreover antipsychotic drugs blocked these effect [Carlsson and Lindqvist, 1963]. Amphetamine was found to stimulate dopamine outflow, while, in contrast, antipsychotics blocked dopamine receptors Van Rossum [1967]. Subsequently, imaging studies demonstrated that acute administration of amphetamine induced greater striatal dopamine release in schizophrenia patients compared to healthy controls [Laruelle et al., 1996]. Together these observations have provided the basis for the dopamine hypothesis of schizophrenia.

Methamphetamine. In the 1990s, there was an epidemic of methamphetamine (sometimes termed ice or crystal meths) use in South-East Asia [UNODC Annual report, 2009], which produced a rapid rise in methamphetamine psychosis in the same region [Peleg-Raibstein et al., 2009]. Subsequently, both its use and its associated psychosis spread to Australia and the USA. Chen et al. [2003] recruited 163 people with methamphetamine psychosis in Taiwan, and reported that in most cases the paranoid symptoms slowly disappeared following cessation of the drug; however, in a proportion they did not remit so readily, if ever. Chen et al. subsequently addressed the question of what was special about those methamphetamine users who became psychotic. Not surprisingly, earlier and greater use of methamphetamine was associated with increased risk of psychosis. More interestingly, methamphetamine users with a pre-existing psychosis-prone personality were more likely to develop frank psychosis as were those with greater familial risk; these two characteristics were also associated with a more prolonged psychotic episode in a more recent report [Grelotti et al., 2010].

Tsuang et al. looked for genes that may confer a vulnerability to psychosis consequent upon methamphetamine use. They reviewed 38 genetic association studies, and reported that four genes appeared associated with psychosis: DTNBP1, which codes for

dystrobrevin-binding protein 1; OPRM1, which codes for the mu-opioid receptor; SNCA, implicated in the modulation of dopamine transmission, and a haplotype of SOD2, which encodes a mitochondrial protein important in cellular defense against oxidative damage [Bousman et al., 2009]. It remains to be seen how robust these associations are.

Mechanisms. Generally speaking, amphetamine and methamphetamine produce a psychotic illness after repeated rather than initial use. Any explanatory theory has to explain this and also why those who have suffered a methamphetamine psychosis can be precipitated back into psychotic illness not only by further methamphetamine abuse by also by social stress. One possibility is dopamine sensitization [Glenthøj and Hemmingsen, 1997]. In rodents, repeated administration of amphetamine leads to reversed tolerance and an increased neurochemical and behavioral reaction to each dose. Boileau et al. [2006] tested whether this might happen also in humans. They administered dextroamphetamine by mouth on days 1, 3, and 5 to 10 healthy volunteers, and measured the effect on striatal dopamine release before exposure, then the day of first exposure, then 2 weeks later after the third dose, using the PET [11C] raclopride technique. Each dose of amphetamine caused greater dopamine release in the ventral striatum together with greater behavioral responses. Indeed, 1 year later there was a greater psychomotor response and greater increase dopamine release compared to the initial dose. Such findings have led to the "dopamine sensitization" hypothesis of schizophrenia which postulates that a sensitized dopamine system is responsible for the genesis of psychotic symptoms [Peleg-Raibstein et al., 2009].

The above studies have generally assumed that amphetamine-induced psychosis is a separate entity from schizophrenia. However, recently a cohort of 42,412 patients with methamphetamine-related conditions were followed-up and compared with individuals with appendicitis; the methamphetamine-using patients were nine times more likely to subsequently receive a diagnosis of schizophrenia [Callaghan et al., 2012]. McKetin et al. [2013] examined the temporal relationship between the methamphetamine use and psychotic symptoms in 278 individuals with methamphetamine dependence. There was a fivefold increase in the likelihood of psychotic symptoms during periods of methamphetamine use relative to periods of no use, this increase being strongly dose-dependent.

Such a transition from transient psychosis to schizophrenia might be a consequence of dopamine sensitization but prolonged methamphetamine abuse may also produce permanent damage to neurons. Thus, a PET study showed a reduction in dopamine transporter density in methamphetamine users, which seemed to be related to the duration of methamphetamine use, and to the chronic psychotic state in methamphetamine users [Iyo et al., 2004].

Khat and its derivatives. Khat is an evergreen shrub, cultivated in the countries around the Red Sea and on the eastern coast of Africa, and chewed for its stimulant effect; for example, in Yemen up to 60% of the males and about 35% of the females chew Khat leaves [Kassim and Croucher, 2006]. Migration of people from the Horn of Africa, and air transport have allowed a much wider distribution to Europe and even North America and Australia. The main psycho-active components of khat are cathinone and cathine [Szendrei, 1980]. Cathinone is most active, and produces effects analogous to those of amphetamine while cathine has a milder action. Normally, fresh leaves contain a higher proportion of the desirable cathinone so Khat is harvested and sold quickly, often wrapped in banana leaves to preserve freshness.

Khat has been shown to induce psychosis in numerous case reports. In 2004, Odenwald et al. [2005] conducted a cross-sectional and case–control study in Somalia. They screened 4,854 persons randomly selected from the general population and identified those with psychotic symptoms. The latter cases had started to use khat earlier in life than control users and had been using khat 8.6 years before positive symptoms emerged; psychotic symptoms often followed a period of binge use. Tulloch et al. [2012] who studied Somali people admitted to a London psychiatric hospital reported that Khat users were especially likely to have attracted a diagnosis of schizophrenia.

"Street dealers" have been replaced by "internet dealers" for certain drugs. Hillebrand et al. [2010] identified 69 European online retailers selling various types of "Legal Highs." This term refers to a broad number of substances "from herbal mixtures to synthetic or 'designer' drugs and 'party pills' [EMCDDA Annual report, 2010]. Although these are psychoactive substances they are legal to supply for purposes other than human consumption. However, their marketing indicates they are intended for the latter. One of the most popular of such internet drugs is Mephedrone, a synthetic cathinone, often known as "Meow meow" or "TopCat" because it is methylmethcathinone [Winstock et al., 2010]. Mephedrone is a stimulant and high doses are reported to be able to cause psychotic episodes [Bajaj et al., 2010]. Recently it has been made illegal in a number of countries.

PCP, Ketamine, and Hypotheses Implicating Glutamate

The "dopamine theory" of schizophrenia has dominated attempts to explain the positive symptoms seen in schizophrenia patients but is less able to account for negative symptoms. Drugs acting on the glutamate system have been proposed to model these [Collins et al., 1960]. Phencyclidine (PCP) was developed as a general anesthetic but unfortunately, up to 50% of adult patients given PCP developed agitation and hallucinations, and consequently so interested shifted to its capacity to produce model psychoses [Luby et al., 1959; Luby et al., 1962]. Acute administration of PCP to healthy volunteers produces disturbances in body image, affect and thinking with similarity to "certain primary symptoms of the schizophrenic process"; as well as impairments of attention, motor function, and proprioceptive acuity [Rosenbaum et al., 1959]. Although PCP was withdrawn from clinical use in 1965, it achieved some modest popularity as a recreational drug sometimes termed "angel dust."

Subsequently, ketamine, another glutamate antagonist, was introduced as an anesthetic, and later reports of ketamine-induced psychosis started to appear. Anis and colleagues showed that ketamine and PCP selectively act at the *N*-methyl-D-aspartate (NMDA) receptor [Anis et al., 1983]. The observation that PCP and ketamine are NMDA antagonists, together with the findings of lower levels of glutamate in cerebrospinal fluid samples from

schizophrenic patients compared to controls, gave rise to the "glutamate hypothesis of schizophrenia" [Kim et al., 1980]. The idea of a glutamatergic abnormality in schizophrenia has attracted increasing interest [Deakin and Simpson, 1997].

According to the glutamate deficiency theory, drugs which enhance glutamate transmission should improve psychotic symptoms. Trials of glutamate potentiation using glycine and related compounds were initially promising [Patil et al., 2007] but ultimately these did not prove efficacious. Nevertheless, researchers theorised that dopamine abnormalities in psychosis could be secondary to a primary hypofunction in glutamate neurotransmission. Seeman and Tallerico [2005] set out to test this latter hypothesis, and found that phencyclidine and ketamine act on the high affinity state of dopamine D_2 receptors, suggesting a dopamimetic action of phencyclidine. Glutamatergic drugs such as glycine transport inhibitors are currently in trials. Most recently, Demjaha et al. [2013] reported that schizophrenic patients who have failed to respond to dopaminergic blockers had no increase in striatal dopamine but increased glutamate in the anterior cingulate. This suggests that there may be separate dopaminergic and glutamatergic types of schizophrenia.

A more negative view of glutamate hypothesis comes from Pomerol et al. who gave ketamine to 10 healthy volunteers. The commonest feature was referential thinking of a delusional nature, together with a range of perceptual abnormalities perhaps best described as dissociative. However, it did not induce hallucinations, and the authors were doubtful about its ability to cause thought disorder; furthermore, although negative-like symptoms resulted they could not exclude the possibility that this was simply due to its anesthetic effects [Pomarol-Clotet et al., 2006]. In a similar vein, Morgan and Curran [2012] who reviewed the literature, noted that ketamine users sometimes reported psychotic symptoms but concluded that "there is little evidence of any link between chronic heavy use of ketamine and a diagnosis of a psychotic disorder."

Cannabis and the Endocannabinoid System

The use of the world's favorite illicit recreational drug, increased in many countries in the latter part of the 20th century; now more than 160 million people take it every day [EMCDDA Annual report, 2009]. Cannabis has been known to produce psychotic symptoms since time immemorial. [Di Forti and Murray, 2005; Murray et al., 2007; Van Winkel et al., 2011], and the mid-nineteenth century the French psychiatrist Moreau de Tour noted the phenomenological similarities between cannabis-induced states and psychosis [Zuardi, 2006].

The first report suggesting that cannabis might be a risk factor for psychosis was the Swedish Conscripts Study in which 45,570 inductees into the military were followed-up for 15 years; the risk for schizophrenia was 2.4 times higher among those who had used cannabis by 18 years than among non-users. Moreover, there was a dose response relationship in that risk for schizophrenia rose to 6.0 times in those who had used cannabis more than 50 times at initial interview [Andreasson et al., 1987]. A series of other epidemiological studies on cannabis use and schizophrenia were published in the early 21st century [Arseneault et al., 2002]. Today consistent evidence supports an association between heavy cannabis use and the risk of psychotic symptoms and illness [Van Os et al., 2002; Zammit et al., 2002; D'Souza et al., 2004; Fergusson et al., 2006; Barnett et al., 2007; Di Forti et al., 2007a, 2009; Moore et al., 2007; McGrath et al., 2010; Zammit et al., 2011; Manrique-Garcia et al., 2012] (Table I).

Meta-analyses report an increase of the risk between 1.4 and 1.9 times in people using cannabis [Moore et al., 2007]. Furthermore, Di Forti et al. [2009] showed a positive association between the frequency of cannabis use, and the potency of the cannabis taken, in increasing the risk of psychotic illness. Synthetic cannabis, or Spice, appears to be especially potent [Auwärter et al., 2009; http://scienceblogs.com/terrasig/2010/02/09/k2-spice-jwh018-marijuana/]. The active substances in Spice are synthetic cannabinoids such as JWH-018 and CP 47,497; a number of cases of spice-induced psychosis have been reported [Every-Palmer, 2011].

Mechanisms. Delta-9-Tetrahydrocannabinol (THC) is the main psychoactive ingredient in natural cannabis; when given experimentally in sufficient dosage, it can produce transient psychotic symptoms and impaired memory via stimulation of CB_1 receptors, targets for the endogenous cannabinoid (endocannabinoid, eCB) transmitters [Matsuda et al., 1990]. THC and synthetic CB_1 agonists elicit psychotic symptoms in a proportion of healthy volunteers [D'Souza et al., 2004; Morrison et al., 2009; Zuurman et al., 2009]. CB_1 receptors are widely distributed throughout the brain, particularly in the hippocampus, amygdala, cerebellum, basal ganglia and pre-frontal cortex [Herkenham et al., 1991; Freiman 2006; Potter 2008]. They are primarily expressed on glutamate and GABA-ergic terminals [Chevaleyre et al., 2006], and upon stimulation by cannabinoids, act to reduce pre-synaptic glutamate or GABA release [Matyas et al., 2008]. The glutamate and GABA inputs to the band of dopamine neurons in the ventral midbrain express CB_1 receptors, and therefore exogenous cannabinoids alter the balance of excitation and inhibition reaching dopamine cells [Lupica and Riegel, 2005; Matyas et al., 2008]. The most commonly documented effect is an increase in firing with attendant elevations of dopamine release at downstream forebrain territories [Melis et al., 2004; Lupica and Riegel, 2005].

An obvious question is, therefore, whether the psychotomimetic properties of THC in humans are mediated via excess dopamine release. Bossong et al. [2009] used the dopamine D_2/D_3 receptor tracer raclopride in a PET study to examine the effect of THC on striatal synaptic dopamine release. The tracer binding was significantly reduced in the ventral striatum and the precommisural dorsal putamen after inhalation of THC compared to placebo, implying the THC provoked an increase in release of endogeneous dopamine in these regions. Another PET study by Stokes and colleagues found only a non-significant increase in dopamine release in the striatum following oral THC [Stokes et al., 2009]. Later Stokes and colleagues re-analyzed their initial data and showed significant decreases in cortical [11C]-raclopride binding potential after administration of THC, suggesting dopamine release in the cortex [Stokes et al., 2010]. Our own group observed clear psychotic phenomena (including thought-echo and passivity) in a group of 10 healthy volunteers given IV THC during SPET scanning but there were no significant differences in DA release between THC and placebo sessions, nor were positive symptoms and DA release related [Barkus et al., 2011].

TABLE I. Selected Studies Which Investigated the Role of Cannabis as a Risk Factor for Schizophrenia in the General Population

Study	N	Design	Prevalence/use of cannabis	Outcome	Adjusted risk
Andreasson et al. [1987]	45,570	Longitudinal conscript Cohort (Sweden)	>50 times	Hospitalisation	2.3
Arseneault et al. [2002]	759	Prospective birth cohort (Dunedin)	Lifetime	Any schizophreniformdisorders	3.1
Van Os et al. [2002]	4,095	Longitudinal population-based (Netherlands)	Lifetime	Any psychotic symptom	2.8
Fergusson et al. [2003]	1,011	Birth cohort (Christchurch)	DSM-IV dependence	Any psychotic symptom	1.8
Zammit et al. [2002]	50,087	Longitudinal conscript Cohort (Sweden)	>50 times	Hospitalisation	3.1
Henquet et al. [2005]	3,467	Prospective cohort (Germany)	Lifetime	Any psychotic symptom	1.7
Di Forti et al. [2009]	280	Case–control (UK)	Lifetime	First episode psychosis	6.8 (high potency users)
McGrath et al. [2010]	3,801	Prospectivecohort (Australia)	≥6 years duration	Nonaffective psychosis	2.1

Most recently, [Kuepper et al., 2012] (personal communication) have shed some light on these seemingly inconsistent findings by showing that while THC does not induce significant increase in striatal dopamine in healthy normals, it does so in patients with schizophrenia and their relatives. This would imply that some families transmit a vulnerability to react in an exaggerated manner to cannabis and its ingredients. Following this line of reasoning, several groups have examined genes involved in the dopamine system which they believed might interact with cannabis use in the production of psychosis. An early report of an interaction between cannabis and COMT [Caspi et al., 2005] has not so far been consistently replicated. However, Van Winkel reported an interaction with AKT1(100), and shortly thereafter this was directly replicated by Di Forti et al. [2012]; if this turns out to be true it would be the first strong evidence for gene x environment interaction in psychosis.

One of the downstream effects of stimulating D_2 receptors in the striatum is the synthesis and release of endocannabinoid transmitters [Giuffrida et al., 1999; Kreitzer and Malenka, 2005] at the dendritic spines of medium spiny neurons (MSNs) [Yin and Knowlton, 2006]. In turn, eCBs act in a retrograde fashion to inhibit neighboring GABA and glutamate terminals [Gerdeman et al., 2002; Robbe et al., 2002; Uchigashima et al., 2007]. There is accumulating evidence that a number of key physiological processes within the striatum depend upon $D_2 \rightarrow$ eCB $\rightarrow CB_1$ signaling and the subsequent modification of fast amino-acid based transmission [Kreitzer and Malenka, 2008; Adermark et al., 2009]. Such processes are believed to be vital for the selection and initiation of psychomotor behaviors and for associative learning, or in other words, the normal functions of the striatum in health [Yin and Knowlton, 2006; Calabresi et al., 2007; Houk et al., 2007; Kreitzer and Malenka, 2007]. One question which arises is whether the pro-psychotic effects of not just THC, but stimulant drugs as well involve the striatal $D_2 \rightarrow$ eCB $\rightarrow CB_1$ trans-synaptic pathway. If this were the case then it might explain why D_2 blockade has little effect on THC psychosis because THC "enters" the pathway at a point which is distal to D_2 receptors. In contrast pharmacological manipulations at CB_1 would be predicted to impact upon stimulant, (D_2 initiated), psychosis, since CB_1 is downstream of D_2.

It is clear that stimulant sensitization or adaptations to repeated drug administration as opposed to single drug exposures, are important for the emergence of psychosis. One of the outcomes of repeated stimulant administration is a functional up-regulation of striatal CB_1 receptors [Graybiel, 2005]. Furthermore, several recent studies have shown that either CB_1 knockout or blockade of CB_1 receptors by potent CB_1 antagonists impairs stimulant sensitization [Centonze et al., 2007; Corbille et al., 2007; Thiemann et al., 2008a], and microinjections of a potent CB_1 antagonist directly into the ventral striatum reduced the expression of behavioral sensitization to methamphetamine [Thiemann et al., 2008b]. Findings with the first generation CB_1 blocker rimonabant in sensitization paradigms have been inconsistent [Lesscher et al., 2005; Chiang and Chen, 2007], but rimonabant, as opposed to newer CB_1 antagonists, only partially blocks the effects of THC in humans [Huestis et al., 2001]; this might explain why an early trial of rimonabant in schizophrenia failed [Meltzer et al., 2004].

Another cannabinoid manipulation has shown more promise. Cannabidiol (CBD), a constituent of free-growing, natural "Cannabis sativa" (but largely eliminated from high potency cannabis preparations such as skunk) (124) appears to have anxiolytic and possibly antipsychotic properties in humans [leweke 2000; Zuardi et al., 2008]. At low doses, the receptor pharmacology of CBD involves pharmacological antagonism of CB_1 agonists (despite low affinity for the orthosteric site of CB_1 receptors) and inhibition of adenosine re-uptake. CBD also inhibits the degradation of the endocannabinoid molecule anandamide and acts at a "third" cannabis receptor termed GPR55 [Pertwee, 2008]. CBD displays efficacy against stimulant [Zuardi et al., 1991; Moreira and Guimaraes, 2005] and NMDA models of psychosis in animals [Long et al., 2006], and against L-DOPA, ketamine [Bosi et al., 2003] and THC elicited psychosis in humans [Zuardi et al., 1982; Bhattacharyya et al., 2009]. A trial of CBD versus amisulpride in 42 schizophrenic patients found equivalent efficacy [Leweke, 2009], but further data, particularly over the longer term, is required before we can conclude that these antipsychotic effects are real.

Overall, the above suggests a model in which pharmacological manipulations to neurochemical systems controlling traffic through striatal circuits can be either pro- or anti-psychotic. The most notable feature is the consistency of the pharmacology with which facilitating the $D_2 \rightarrow eCB \rightarrow CB_1$ axis appears to be pro-psychotic.

CONCLUSIONS

It is clear from the literature we have reviewed that the major neurochemical theories of schizophrenia have their origins in investigations into the effects of drugs of abuse. Research into the effects of LSD initiated the serotonergic model; amphetamines the dopamine hypothesis, PCP and ketamine the glutamatergic model, while most recently the effects of cannabis have provoked interest in the role of endocannabinoids. None of these models account for the complete picture of schizophrenia, but this is not to be expected if we regard the condition as one with multiple causes and consequent clinical heterogeneity. Rather the various drug models mimic different aspects of the syndrome. Stimulants and THC are particularly likely to induce paranoia beliefs [Leweke, 2009], whereas LSD is more closely associated with visual illusions/hallucinations [Javitt and Zukin, 1990; Gonzalez-Maeso and Sealfon, 2009]. The non-competitive NMDA antagonists phencyclidine (PCP) and ketamine appear to induce negative symptoms, and oneiroid states (characterized by perceptual illusions, perplexity and delusional thinking in the context of clouding of consciousness) [Smith et al., 2009]. What is common between the different classes of drug is the promotion of a fundamental change in the subject's experience of reality, whether acutely, during drug intoxication (in the case of LSD, ketamine and THC) or as a result of an adaptive process secondary to repeated use (stimulants and THC).

However, is it possible to discriminate between drugs which distort the experience of reality in a way which closely corresponds to aspects of schizophrenia from those that do not? One approach is to postulate that if administration of a drug pushes the individual into expressing psychotic symptoms AND if it is also "true" that a diametrically opposing pharmacological manipulation pulls a schizophrenic-psychosis back into reality, then the drug-model in question constitutes a reasonable model of schizophrenic-like psychosis. Some examples may illuminate this. Agonists at the 5HT receptor transform reality in a fundamental way; yet 5HT2 antagonists have no efficacy against schizophrenic psychosis. Similarly, NMDA channel blockers distort the experience of reality, yet, despite much effort and theoretical support, drugs which enhance NMDA channel opening have not yet been proven to be effective in schizophrenia. In contrast, opposing pharmacological manipulations at D_2 receptors can elicit clear bi-directional responses at the psychological level. Drugs which drive D_2-mediated signaling to excess have pro-psychotic properties *AND* D_2 blockers are effective against schizophrenic psychosis. On this basis, one can infer that, at a neurochemical level, the DA model psychosis more accurately simulates the reality-distortion in schizophrenia than are either the serotonergic or glutamatergic models.

In recent years, it has been suggested that excess dopamine synthesis and release in the striatum is the final, common arbiter of positive psychotic symptoms [Broome et al., 2005; Di Forti et al., 2007b; Murray et al., 2008] probably through a pathological dysfunction of the "reward" pathway. Do all of the drugs which induce psychotic symptoms do so via their effects on the dopamine system? Certainly, as we have seen, an argument can be made that they all impact on the dopamine system either directly or indirectly. However, it is not clear that this effect accounts for their propensity to induce the characteristic positive symptoms of schizophrenia. Another caveat is that the dopamine model can probably no longer be considered in isolation from the emerging endocannabinoid model. Earlier we made use of the relatively simple concept of a $D_2 \rightarrow eCB \rightarrow CB_1$ axis to describe the known physiological relations of the two neurochemical systems within the striatum. Notably, opposing pharmacological manipulations at CB_1 receptors can also elicit bi-directional responses, either pro- or anti-psychotic. Moreover, CB_1 manipulations appear to be effective against dopamine D_2 mediated psychoses.

Not all addictive drugs which impact on the dopamine system appear to be able to induce psychotic symptoms. For example, the use of opiates or benzodiazepines does not induce psychotic symptoms. One possible reason is that the fact that nicotine and opiate receptors (and responses) show a rapid de-sensitization following exposure to their respective agonists. Most would say that cigarette smoking similarly does not induce psychosis but some are beginnings to question this. This illustrates the general theme of this paper; determining the neurochemical differences between those drugs whose effects do and which do not mimic particular aspects of schizophrenia is worthy of investigation in humans as well as in animals. Furthermore, there is increasing interest in such questions partly driven by the evidence that substance-induced psychotic disorders predict schizophrenia spectrum disorders to a greater extent than was previously thought [Niemi-Pynttari et al., 2013].

A dissenting view on glutamate hypothesis comes from Pomerol et al. who gave ketamine to 10 healthy volunteers.

The first study suggesting that cannabis might be a risk factor for psychosis came from the Swedish Conscripts Study in which 45,570 inductees into the military were followed-up for 15 years; the risk

for schizophrenia was 2.4 times higher among those who had used cannabis by 18 years than among non-users. Moreover, there was a dose response relationship in that risk for schizophrenia rose to 6.0 times in those who had used cannabis more than 50 times at initial interview [Andreasson et al., 1987]. A series of other epidemiological studies on cannabis use and schizophrenia were published in the early 21st century [Arseneault et al., 2002]. Today consistent evidence supports an association between heavy cannabis use and the risk of psychotic symptoms and illness [Van Os et al., 2002; Zammit et al., 2002; D'Souza et al., 2004; Fergusson et al., 2006; Barnett et al., 2007; Di Forti et al., 2007b, 2009; Moore et al., 2007; Van Os 2008; Kuepper and Van Os, 2012; McGrath et al., 2010; Zammit et al., 2011; Manrique-Garcia et al., 2012].

Finally, not all addictive drugs which impact on the dopamine system appear to be able to induce psychotic symptoms. For example, the use of opiates or benzodiazepines does not induce psychotic symptoms. One possible reason is that the fact that nicotine and opiate receptors (and responses) show a rapid desensitization following exposure to their respective agonists. Most would say that cigarette smoking similarly does not induce psychosis but some are beginnings to question this. This illustrates the general theme of this article; determining the neurochemical differences between those drugs whose effects do and which do not mimic particular aspects of schizophrenia is worthy of investigation in humans as well as in animals.

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