Review

Biological Psychiatry

Human Laboratory Studies on Cannabinoids and Psychosis

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ABSTRACT

Some of the most compelling evidence supporting an association between cannabinoid agonists and psychosis comes from controlled laboratory studies in humans. Randomized, double-blind, placebo-controlled, crossover laboratory studies demonstrate that cannabinoid agonists, including phytocannabinoids and synthetic cannabinoids, produce a wide range of positive, negative, and cognitive symptoms and psychophysiologic deficits in healthy human subjects that resemble the phenomenology of schizophrenia. These effects are time locked to drug administration, are dose related, and are transient and rarely necessitate intervention. The magnitude of effects is similar to the effects of ketamine but qualitatively distinct from other psychotomimetic drugs, including ketamine, amphetamine, and salvinorin A. Cannabinoid agonists have also been shown to transiently exacerbate symptoms in individuals with schizophrenia in laboratory studies. Patients with schizophrenia are more vulnerable than healthy control subjects to the acute behavioral and cognitive effects of cannabinoid agonists and experience transient exacerbation of symptoms despite treatment with antipsychotic medications. Furthermore, laboratory studies have failed to demonstrate any "beneficial" effects of cannabinoid agonists in individuals with schizophrenia—challenging the cannabis self-medication hypothesis. Emerging evidence suggests that polymorphisms of several genes related to dopamine metabolism (e.g., *COMT*, *DAT1*, and *AKT1*) may moderate the effects of cannabinoid agonists in laboratory studies. Cannabinoid agonists induce dopamine release, although the magnitude of release does not appear to be commensurate to the magnitude and spectrum of their acute psychotomimetic effects. Interactions between the endocannabinoid, gamma-aminobutyric acid, and glutamate systems and their individual and interactive effects on neural oscillations provide a plausible mechanism underlying the psychotomimetic effects of cannabinoids.

Keywords: Cannabinoids, Cannabis, CB_1R, Cognition, Dopamine, Experimental, GABA, Glutamate, Laboratory, Psychosis, RCT, Schizophrenia, THC

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Converging lines of preclinical, epidemiologic, and experimental evidence support an association between cannabinoid agonists and psychosis. The rich literature on human laboratory studies (HLS) with cannabis and cannabinoids such as Δ^9-tetrahydrocannabinol (THC) includes several studies that have specifically examined outcomes relevant to psychosis. This article reviews HLS with cannabinoids with a focus on outcomes relevant to psychosis. We first present a brief overview of advantages and disadvantages of HLS that should permit the reader to evaluate the data in an informed manner.

OVERVIEW OF HUMAN LABORATORY STUDIES

HLS can complement epidemiologic studies of cannabinoids and address some of their limitations. First, the temporal distance between cannabis exposure and psychosis outcomes in epidemiologic studies limits interpretation with regard to causality. HLS can demonstrate psychosis outcomes tightly time locked to cannabinoid exposure. Second, the variability in the THC content of cannabis, the typical practice of sharing cannabis, and the variable pharmacokinetics associated with oral and inhaled consumption make it challenging to establish precise dose-response relationships. In HLS, the dose and delivery can be controlled, and dose-response relationships can be evaluated. Third, in contrast to epidemiologic studies, HLS permit isolating the effects of individual cannabinoids (e.g., THC and cannabidiol [CBD]). Fourth, in epidemiologic studies, it is difficult to tease out the risk for psychosis outcomes conferred by preexisting factors from the risk associated with cannabis exposure. HLS address this difficulty to some extent by carefully screening out subjects with any obvious risk for psychosis. Finally, in surveys, individuals with psychotic disorders report benefits from using cannabis. In contrast to surveys that rely on retrospective self-report that are susceptible to denial and rationalization, in HLS both subjective and objective data can be collected in real time.

The aforementioned strengths notwithstanding, HLS are not without limitations. First, to enhance safety, HLS typically exclude individuals with an obvious risk of psychosis (1).

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Furthermore, people who experience unpleasant effects with recreational cannabis use are not likely to volunteer for HLS. Thus, study-imposed selection and subject self-selection may limit the generalizability of the results of HLS. Second, although a wide range of outcome measures can be studied, there are limitations to the capacity of any drug to mimic a psychotic disorder accurately. Psychotic disorders are often heterogeneous, evolve over time, and may involve neurodevelopmental or neurodegenerative processes (or both). Therefore, it is unlikely that the administration of any single pharmacologic agent to healthy subjects would fully replicate all elements of a psychotic disorder. Moreover, although HLS capture psychometrically defined psychosis (e.g., as measured by the Positive and Negative Syndrome Scale), they typically do not induce clinical psychosis in healthy subjects. Thus, HLS with cannabinoids might be useful in probing the contributions of the endocannabinoid system to discrete components of psychosis, rather than the disorder as a whole.

REVIEW OF HLS OF CANNABINOIDS IN HEALTHY SUBJECTS

Over the past several decades, there has been a surge in HLS initially with cannabis and then with THC, a cannabinoid type 1 receptor (CB_1R) agonist and constituent of cannabis; synthetic CB_1R agonists, dronabinol and nabilone; and CBD, another prominent component of cannabis. This review is focused on HLS with outcomes relevant to psychosis. A search on the PubMed database was done in October 2015 using the search filters: Species: Humans; Article type: Clinical trial; and Key words: psychosis and one of the following: cannabinoids (32 results), tetrahydrocannabinol (31 results), cannabidiol (8 results), cannabis (76 results), nabilone (1 result), dronabinol (30 results), and rimonabant (3 results). These articles were individually reviewed. Leads from the review of these articles were also reviewed. Results that were included were in English, used HLS as the methodology, and had outcome measures related to psychosis. This search identified 68 studies, which are listed in Tables S1 and S2 in Supplement 1. Table 1 summarizes the HLS sorted by commonly used psychosis-relevant outcome measures.

SUBJECTIVE AND BEHAVIORAL EFFECTS

Positive Symptoms

Cannabis extracts as well as THC alone produce a range of transient, positive symptoms, including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations measured on standardized rating scales such as the Positive and Negative Syndrome Scale, Clinician Administered Dissociative States Scale, Psychotomimetic States Inventory, and Brief Psychiatric Rating Scale. Although these effects manifest across a range of doses and routes of administration, they are dose dependent and have a distinct time course depending on the route of administration (2–6). In one of the first controlled HLS with intravenous (IV) THC, D'Souza *et al*. (2) administered two doses (2.5 mg and 5 mg) to healthy adults ($n = 22$) in a double-blind, randomized, placebo-controlled, crossover design. The THC produced transient positive psychotic symptoms, including perceptual alterations. These results were replicated by Morrison *et al.* (4) in a similar study. Several other HLS using IV doses of THC of 1.25–3.5 mg administered over 10–20 minutes demonstrated similar acute transient psychotomimetic effects (7–13). Finally, the synthetic THC analogues nabilone and dronabinol produce a similar profile of effects and disrupt performance on a visual information-processing task, binocular depth inversion illusion, a surrogate marker of psychosis (14–16). This effect on binocular depth inversion illusion has also been shown with cannabis resin (17).

Psychosis-Relevant "Positive Symptoms" Induced by THC Compared With Effects of Other Drugs in HLS. There are no head-to-head comparisons of the psychosis-relevant effects of cannabinoids and other drugs, such as amphetamine, lysergic acid diethylamide, psilocybin, and salvinorin A. Furthermore, there are challenges to comparing drugs that have different mechanisms of action. Studies at our center conducted under similar conditions along with reports from other laboratories permit limited comparisons (Figure 1) (2,18,19). Although ketamine and THC induced a similar magnitude of positive symptoms in healthy subjects, there were qualitative differences in their psychosis-like effects. In contrast to THC, ketamine was less likely to produce paranoia, whereas amphetamine did not produce negative symptoms. Salvinorin A, lysergic acid diethylamide, and psilocybin produced predominant visual perceptual alterations. Finally, in contrast to ketamine, amphetamine, and salvinorin A, the acute effects of THC were delayed and developed over 10–15 minutes.

Interactions With CBD. The second most prominent cannabinoid in cannabis is CBD. In contrast to THC, CBD displays CB_1R antagonism/inverse agonism among several other modulatory effects on the endocannabinoid system. The potential antipsychotic effects of CBD have drawn increasing attention (20), and some HLS have examined the interactive effects of THC and CBD. Pretreatment with CBD is associated with lower THC-induced psychotomimetic effects, paranoia, and verbal memory impairments (12,21). Furthermore, during processing of fearful faces, THC resulted in increased psychotic symptoms and skin conductance responses, whereas CBD led to a reduction in anxiety and a decrease in skin conductance response (22). Also, THC and CBD had opposite effects on blood oxygen–level dependent responses in tasks of verbal recall, response inhibition, processing fearful facial expressions, auditory processing, and visual processing (Table S2 in Supplement 1) (12).

Negative Symptoms

The THC-induced negative effects, similar to the negative symptoms of schizophrenia, although studied less frequently than positive symptoms, include blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport (2,3). Furthermore, Morrison and Stone (3) demonstrated that the THC-induced negative symptoms were not a consequence of its sedating and cataleptic effects.