Psychotomimetic Effects of Kappa Opioid Receptor Agonists

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The κ opioid receptor (KOR)-dynorphin system has been implicated in the pathogenesis and pathophysiology of affective disorders, drug addiction, and psychotic disorders (1). Within the brain, KOR expression is highest in regions implicated in the modulation of reward, mood, cognition, and perception (ventral tegmental area, nucleus accumbens, prefrontal cortex, hippocampus, striatum, amygdala, and hypothalamus). Accordingly, drugs directed at KOR as either antagonists or partial agonists have potential utility for a number of indications, especially as antidepressants and anxiolytics. Additionally, KOR agonists are gaining attention as potential antiaddiction medications and analgesics without a high abuse potential. However, the adverse effects produced by KOR agonists including aversion, sedation, dysphoria, and hallucinations have limited their clinical use. Understanding how KOR signaling discriminates between analgesia and the unwanted side effects may lead to the design of more successful therapies. Furthermore, understanding the molecular events involved in KOR-mediated hallucinations will enhance our understanding of cognition and perception.

The hallucinogenic plant *Salvia divinorum* (salvia) has recently gained attention for its increasing recreational use among young people (1). Traditionally, *S divinorum* has been used for its psychoactive properties in religious and medicinal rituals by the Mazatecs of Oaxaca, Mexico. Salvinorin A (SA) is the psychoactive compound in *S divinorum* and is a highly potent KOR selective agonist with no affinity for any other known neurotransmitter systems (2). Other classical hallucinogens such as lysergic acid diethylamide and psilocybin have complex pharmacologies, but their psychedelic actions are mediated mainly via 5-hydroxytryptamine (5-HT_{2A}) serotonin receptors (3). The discovery that SA is a KOR-selective hallucinogen was exciting because it implied a role for the KOR in cognition and perception and supported the notion that the KOR system could be involved in disorders of perception such as schizophrenia and psychosis. Therefore, the KOR system provides another pathway for studying human cognition as well as psychosis. However, controlled clinical studies documenting the effect of SA in humans have been limited and primarily anecdotal.

Pfeiffer *et al.* (4) were the first to implicate KOR receptors in human psychotomimesis. They reported that both the dysphoric and psychotomimetic effects of the benzomorphan KOR agonist MR 2034 were blocked by naloxone, suggesting that the effects were mediated via KOR signaling. Since then, dysphoria has been considered the best surrogate marker of KOR agonism, whereas the hallucinogenic effects of KOR agonists have been relatively unexplored. In this issue of *Biological Psychiatry*, Ranganathan *et al.* (5) explored the psychotomimetic effects, perceptual alterations, neuroendocrine effects, and quantitative electroencephalographic (EEG) effects resulting from the controlled administration of SA to humans. This study provides the first comprehensive evaluation of the effects of SA in a randomized, double-blind, placebo-controlled, crossover, counterbalanced study in healthy humans.

To perform this study, Ranganathan *et al.* (5) recruited 10 psychiatrically and medically healthy subjects who had previous experience with SA and, in some cases, other psychoactive medications. The human subjects inhaled one of two doses of SA or placebo, and several parameters were measured including EEG, cognitive testing, and neuroendocrine studies.

Consistent with anecdotal reports, the subjects experienced a rapid, short-lasting, and intense psychoactive effect of SA. The subjects described feelings of dissociation and detachment, changes in their awareness of visual or auditory stimuli, and mood alterations. Both high (12 mg) and low (8 mg) doses of SA produced psychotomimetic effects as assessed by the Positive and Negative Syndrome Scale positive subscale and the Psycholotomimetic States Inventory relative to placebo. The authors noted that magnitude of the psychotomimetic effects of SA measured by the Positive and Negative Syndrome Scale-positive subscale and Psycholotomimetic States Inventory are similar to the effects of ketamine and Δ-9-tetrahydrocannabinol. Furthermore, changes in perceptual alterations were observed with the Hallucinogen Rating Scale. However, no change in perception was observed with the Clinician Administered Dissociative Symptoms Scale, and no changes in cognition were detected by the digit forward, digit backward, and letter number sequencing test. The absence of more robust alterations in perception and cognition could be due to a lower dose than what is used recreationally. Furthermore, the subjects did not report any lasting or recurrent effects of SA during safety follow-up examinations.

To gain a better understanding of the endocrine effects of SA, the authors measured the cortisol and prolactin serum levels after SA administration. The low dose of SA elevated plasma cortisol, and both doses of SA elevated prolactin levels of both returned to baseline 60 minutes after SA administration. KOR agonists have been shown to raise prolactin serum levels in rats and primates, but this study is the first to report this effect in humans. The proposed mechanism for the increase in serum prolactin levels is the KOR-induced modulation of dopamine in the hypothalamic tuberoinfundibular system (5). Additionally, cortisol levels are known to increase in animals and humans as a result of KOR agonists, although it is interesting that only the low dose of SA increased the cortisol levels in humans during this study. The authors conclude that KOR agonists may stimulate the activity of the hypothalamic-pituitary axis in humans to alter the levels of cortisol. The neuroendocrine effects of SA in this study are consistent with previous studies that suggest what brain regions may be responsible for the physiological outcomes of KOR agonism. Nonetheless, further studies are required to elucidate the circuitry involved in mediating the psychotomimetic effects of KOR agonists.

Resting EEG power is sensitive to drug-induced changes in consciousness and may be altered in psychosis. The authors reported

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that both doses of SA decreased resting-state EEG spectral power compared with the placebo. The psychophysiologic effects of SA are consistent with a previous human study that shows pentazocine, a KOR agonist, reduces EEG power (5). Ranganathan *et al.* (5) noted that the pattern of SA-induced effects is different from that of other hallucinogens such as ketamine, mescaline, and ayahuasca that result in either unchanged or increased EEG power. This observation supports the idea that the mechanism of KOR-mediated hallucinations may differ from other hallucinations.

The authors did not comment on any sex differences in SA effects. It is known that KOR agonists have sex differences in analgesia in humans (6). It would be interesting to examine whether any sex differences are observed for the other effects of SA measured here. Additionally, it would be interesting to examine the effects of the doses used in this study compared with a recreational dose. Because the participants reported that the effects were only 20–30% that of a recreational dose, it is possible that some findings may differ between the 8–12 mg dose and a recreational dose. Additionally, the use of a higher dose that is similar to a recreational dose may allow for the observation of a dose-dependent effect of SA.

The authors noted that the effects of SA make it unlikely to cause addiction, which is likely a result of KOR agonists' aversive effects. Additionally, addictive drugs are known to enhance dopaminergic release nucleus accumbens, whereas SA inhibits dopamine release (7). In this regard, KOR agonists may have potential antiaddictive properties because not only do they inhibit dopamine release, but they also antagonize cocaine-induced behaviors including self-administration (8). Additionally, because of their low dependence potential, KOR agonists are also being pursued as pain therapies, although their dysphoric and hallucinogenic effects have limited their therapeutic potential. Relevant to this issue is the phenomenon of functional selectivity whereby ligands differentially alter downstream signaling events including G-protein and β-arrestin signaling (9). Thus, for instance, Bruchas *et al.* (10) concluded that the dysphoric effect of KOR agonists is mediated solely through β-arrestin signaling, whereas the analgesic actions are apparently due to canonical G-protein signaling. Given this, $G\alpha_i$-biased KOR agonists may maintain analgesia without inducing dysphoria. Furthermore, because of the diverse structure of KOR ligands, there is potential to discover a variety of functionally selective ligands that can be used to probe KOR signaling as well as improve KOR-based therapeutics.

Most importantly, this study extends our knowledge of drug-induced psychotomimesis. Previously, several neurotransmitter systems including glutamatergic, dopaminergic, and serotonergic neuronal signaling have been implicated in the psychotomimetic actions of drugs such as ketamine, amphetamines, and lysergic acid diethylamide, respectively. Because SA reduces dopamine release and SA apparently has activity only at the KOR, these results imply a potentially potent role for KOR in the pathophysiology of psychosis. Identifying the neuronal circuitry and signaling mechanisms responsible KOR agonist-induced psychosis may lead to a better understanding of psychosis and enhance the potential for better antipsychotic therapies.

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