Salvinorin A: the ‘magic mint’ hallucinogen finds a molecular target in the kappa opioid receptor

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Salvinorin A, a neoclerodane diterpene, is the most potent naturally occurring hallucinogen known and rivals the synthetic hallucinogen lysergic acid diethylamide in potency. Recently, the molecular target of salvinorin A was identified as the kappa opioid receptor (KOR). Salvinorin A represents the only known non-nitrogenous KOR selective agonist. Based on the selectivity of salvinorin A for the KOR, this receptor represents a potential molecular target for the development of drugs to treat disorders characterized by alterations in perception, including schizophrenia, Alzheimer’s disease and bipolar disorder.

Salvia divinorum (Diviner’s sage) (Fig. 1a) is a rare member of the mint family that has been used for many centuries by the Mazatec people of Oaxaca, Mexico in traditional spiritual practices (Box 1). More recently, S. divinorum (also known as ‘magic mint’) has been used as a marijuana substitute by Mexican youths [1]. Furthermore, a large number of S. divinorum plants were discovered recently in Swiss horticulturists’ greenhouses and a few more were seized at a large-scale plantation in Switzerland, implicating their increasing use as a recreational drug in Europe [2]. For several years, S. divinorum has been cultivated in California for use as a legal hallucinogen. At present, neither Swiss nor US laws for controlled substances ban the use of S. divinorum or its active compounds. In traditional spiritual practices, S. divinorum is typically ingested by one of three routes: (1) mastication and swallowing of the leaves; (2) crushing the leaves to extract the juices and then swallowing the extract; or (3) smoking the leaves [3]. The hallucinatory effect that results has been reported to be potent and intense, lasting for up to an hour [1,3].

The presumed main active ingredient of S. divinorum salvinorin A (Fig. 1b) was first identified by Alfredo Ortega in 1982 and independently isolated by Leander Valdes soon thereafter [1,4]. Salvinorin A is a neoclerodane diterpine of known absolute stereochemistry whose structure has been determined using ¹H nuclear magnetic resonance (NMR) and by two independent single-crystal X-ray studies (Fig. 1c) [4–6]. Salvinorin A represents the only known psychoactive terpenoid [7] and is chemically unique. Additionally, salvinorin A has been reported to be the most potent naturally occurring hallucinogen, with an effective dose, when smoked, of 200–1000 μg in humans. Thus, it is similar in potency to the synthetic hallucinogens lysergic acid diethylamide [LSD (the typical human dose used in abuse is 50–250 μg)] and 4-bromo-2,5-dimethoxyphenylisopropylamine [DOB (the typical human dose used in abuse is 500–1000 μg)] [1,3].

The molecular target of salvinorin A

Previous attempts to determine the proximal molecular target(s) of salvinorin A have been unsuccessful. Shortly after the recognition of the psychoactive properties of salvinorin A (by Daniel Siebert in 1994), salvinorin A was submitted for screening to NovaScreen™ to discover its molecular target [3]. Unfortunately, salvinorin A showed no significant inhibition of radioligand binding at any of the receptors, including various biogenic amine receptors, cannabinoid receptors and sigma receptors, screened by the NovaScreen™ process [3]. Recently, the pharmacological profile of salvinorin A at a variety of human G-protein-coupled receptors (GPCRs), ligand-gated

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**Fig. 1.** (a) Salvia divinorum is a rare member of the Lamiaceae (mint) family. It has been used in traditional spiritual practices and as a recreational drug. (b) The two-dimensional structure of salvinorin A, the presumed main active ingredient of S. divinorum. (c) The three-dimensional structure of salvinorin A.

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Box 1. The ethnopharmacology of *Salvia divinorum*

*Salvia divinorum* is known by many names including ska Maria, ska Pastora, hojas de Maria, hojas de la Pastora, hierba Maria, and la Maria. These names reflect the Mazatec belief that *S. divinorum* is the incarnation of the Virgin Mary; hence, the plant is highly prized and respected [16–18]. Despite its many names, *S. divinorum* was not identified until 1962 when Wasson and Hofmann collected a member of the Lamiaceae (mint) family that was known by the Mazatec people of Oaxaca, Mexico to have psychoactive properties [19]. This mint only grows in forest ravines and in other moist areas of the Sierra Mazateca between 750 m and 1500 m altitude [16].

Interestingly, *S. divinorum* flowers rarely, blossoming with white corollas and purple chalyses [16]. Seed production is even more rare because *S. divinorum* has never been reported to produce seeds in its native habitat of the Sierra Mazateca. Indeed, only Valdes and Siebert have reported the identification of seeds. *S. divinorum* primarily reproduces by vegetative growth from a shoot that is stuck into the ground, and can be readily grown from cuttings. Some believe that all *S. divinorum* strains present in the USA are one of seven vegetatively propagated clones, originating from the Sierra Mazateca in Oaxaca, Mexico. Most clones in the USA are derived from the original clone identified by Wasson in 1962 [18,20]. Because *S. divinorum* grows easily from cuttings, there is great potential for its increased use as a recreational drug; a yield of even a gram of salvinorin A per kilogram of dried leaves would provide 2000 doses of salvinorin A [21]. For additional information on *S. divinorum* and salvinorin A, see ‘The Salvia divinorum Research and Information Center’ (http://www.sagewisdom.org), an online resource maintained by Daniel Siebert.

KOR antagonists as therapeutic agents?

KOR agonists have been shown previously to be psychotomimetic [9] and the psychoactive properties of salvinorin A in humans are probably mediated by KORs. Indeed, there is one anecdotal report that the hallucinogenic effects of salvinorin A are blocked by pretreatment with naltrexone, a nonspecific opioid receptor antagonist with modest affinity for KORs (D. Siebert, pers. commun). Thus, overdoses of salvinorin A are likely to respond to naltrexone (Narcan®) or naltrexone administration. There are numerous diseases characterized by hallucinations, including schizophrenia, depression with psychotic features, and the hallucinosis associated with certain dementias such as Alzheimer’s, Huntington’s and Pick diseases. Diseases characterized by hallucinosis could, conceivably, reflect alterations in KOR number or KOR signal transduction; thus, KOR selective antagonists might represent novel therapeutic targets for diseases in which hallucinations are prominent [11]. However, there are few examples in the literature to corroborate this hypothesis. For example, administration of naltrexone and naltrexone to schizophrenics showed only modest results [12]. Clearly, further studies using KOR selective antagonists are warranted, although it is

Chemical name

U69593: (S)-[[N-(7,8-epoxy-7,8-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-N-methyl-N-[7-(1-pyrrolidinyl)7-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide

http://t1ps.trends.com
possible that KOR selective antagonists will have no efficacy in diseases manifested by psychosis. Intriguingly, two independent post-mortem studies of Alzheimer’s disease have reported an upregulation of KOR expression in the amygdala, putamen and cerebellar cortex [13,14]. In these same studies, the expression of MORs and DORs remained unchanged or was downregulated in these regions [13,14].

Concluding remarks
Salvinorin A represents a new class of non-nitrogenous KOR selective agonists, and KORs and/or KOR signaling probably play a role in the modulation of human cognition and perception. Because salvinorin A, a KOR selective agonist, has psychoactive properties, KOR selective antagonists could conceivably prove useful in the treatment of certain psychiatric disorders (e.g. Alzheimer’s disease, schizophrenia, bipolar disorder and dementia). Previous development of antipsychotic drugs has primarily focused on the 5-HT2A and the D2 dopamine receptor [15]. Knowledge that the KOR mediates the hallucinatory effects of salvinorin A provides a novel molecular candidate for the development of antipsychotic drugs.

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