



Current Topics

Salvinorin A: A novel and highly selective κ -opioid receptor agonist

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Abstract

κ -opioid receptors (KORs) represent the principal site of action of dynorphin and related neuropeptides. Recently, Salvinorin A—a naturally occurring neoclerodane diterpene hallucinogen was identified to be a highly selective KOR agonist. In this brief review we summarize the known chemistry, pharmacology and biology of salvinorin A. Because salvinorin A profoundly alters human consciousness and perception, a study of how salvinorin A exerts its actions on KORs may yield novel insights into the molecular and cellular basis of uniquely human higher cortical functions.

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Introduction

Historically, opioid receptor research has focused, mainly unsuccessfully, on the development of analgesic agents with minimal abuse potential (Aldrich and Vigil-Cruz, 2003). Among the various opioid receptor subtypes μ , δ and κ -opioid receptors (KOR's) have been actively targeted because of the likelihood that peripherally-active KOR agonists would have few side-effects and limited abuse

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potential (DeHaven-Hudkins and Dolle, 2004) It has long been recognized, however, that centrally acting KOR agonists might have limited usefulness in humans because of psychotomimetic and dysphoric actions (Pfeiffer et al., 1986; Rimoy et al., 1994; Walsh et al., 2001) although it has been unclear to what extent the ‘psychotomimetic’ or dysphoric actions of KOR agonists are mediated by KOR or other receptors (e.g. σ receptors) (Kumor et al., 1986). Nonetheless, these findings have led some to imply that the kappa-ergic receptor system in humans may serve more to modulate human consciousness than to be involved in the hedonic axis of behavior (Cami and Farre, 2003; Borg et al., 2003). Recently, salvinorin A was identified as a highly selective, highly efficacious KOR agonist (Roth et al., 2002); we suggest that study of salvinorin A’s actions in vivo will help to illuminate the role of the KOR system in humans.

Salvinorin A: a selective and highly efficacious κ agonist

Salvinorin A (Fig. 1) represents the only known non-nitrogenous and selective KOR full agonist (Roth et al., 2002; Chavkin et al., 2004). Salvinorin A is the main active ingredient of the hallucinogenic plant *Salvia divinorum*-a member of the sage family (Valdes et al., 1983; Siebert, 1994). In humans, ingestion of *Salvia divinorum* via mastication of a quid induces a short-lived experience which is distinct from that induced by classical hallucinogens (Wasson, 1962) and which appears to be identical in character to the experience induced by smoking highly purified salvinorin A (Siebert, 1994). An examination of first-person accounts of salvinorin A’s actions in humans has disclosed that salvinorin A induces ‘spatiotemporal dislocation’ rather than a frank hallucinatory experience which is frequently dysphoric in nature (Roth et al., 2004).

We have found that salvinorin A has apparent selectivity for KORs with negligible affinity for any of a large number of receptors, ion channels and transporters which have thus far been profiled.

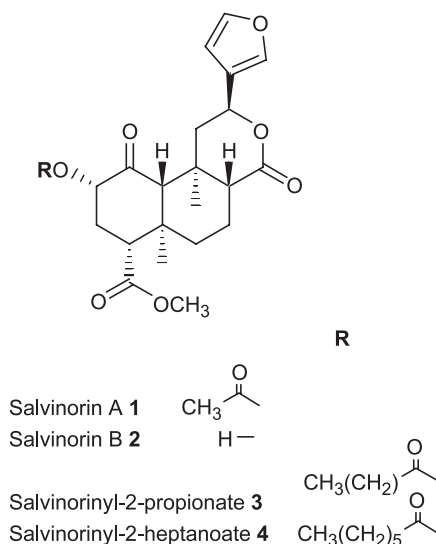


Fig. 1. Structures of Salvinorin A, B and 2-salvinorinyl esters (Chavkin et al., 2004).

Thus, we discovered that salvinorin A has negligible affinity for other known receptors for psychoactive compounds including μ -, δ -, and ORL-opioid receptors, σ_1 and σ_2 -sigma receptors, CB-1 and CB-2 cannabinoid receptors, muscarinic and nicotinic cholinergic receptors, serotonin receptors (including 5-HT_{2A} receptors-the site of action of LSD) and various ionotropic and metabotropic glutamate receptors (Roth et al., 2002; Chavkin et al., 2004).

In terms of salvinorin A's actions on KORs it is a full agonist, being marginally more efficacious than dynorphin 1–13 at activating KORs under conditions of minimal receptor reserve (Chavkin et al., 2004). Interestingly, salvinorin A was significantly more efficacious than either U69, 593 or U50,488-two prototypical KOR agonists frequently used in in vitro and in vivo studies (Chavkin et al., 2004). Taken together, these results indicate that salvinorin A is the most highly efficacious, naturally-occurring, non-peptide KOR agonist.

Limited structure-activity studies have disclosed that the 2'-position of salvinorin A is extremely important for salvinorin A's actions at KORs. Thus, only a limited variety of substitutions were tolerated at the 2'-position (Fig. 1) and the active derivatives (e.g. salvinorinyl-2-propionate; salvinorinyl-2-heptanoate) showed diminished intrinsic efficacy when compared with salvinorin A (Chavkin et al., 2004). Intriguingly, salvinorin B, which could arise from salvinorin A via the esterase-mediated hydrolysis of the 2-acetate group, is inactive. These findings have led to the suggestion that salvinorin A's short actions in vivo might be due to rapid hydrolysis of salvinorin A to salvinorin B (Roth et al., 2004).

The other Salvinorin A analogues: C (Valdes et al., 2001), D–F (Munro and Rizzacasa, 2003) were isolated from the leaves of *Salvia divinorum*. The structures for Salvinorin C–F were characterized, while the activities remain unclear (Fig. 2).

To date, animal studies using salvinorin A have been limited to one published study (Butelman et al., 2004) In this study using subhuman primates, Butelman et al. demonstrated that the discriminative stimulus actions of salvinorin A were identical to those induced by the KOR agonist U69, 593 and distinct from those induced by ketamine-an NMDA antagonist. Additionally, Butelman et al. reported that the actions of salvinorin A were blocked by an opioid antagonist and that a κ -

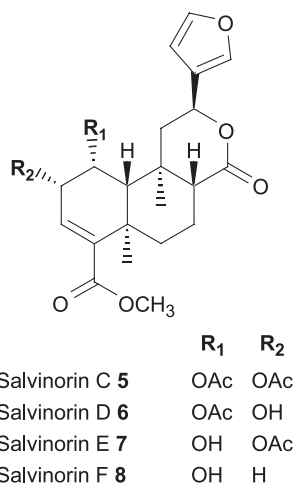


Fig. 2. Isolated natural Salvinorin A analogues from *Salvia divinorum* (Valdes et al., 2001; Munro and Rizzacasa, 2003).

specific antagonist blocked salvinorin A's effects in 2 out of 3 monkeys (Butelman et al., 2004). Preliminary studies performed in collaboration with the Pintar lab (J. Pintar, personal communication) have revealed that the anti-nociceptive actions of salvinorin A seen in wild-type mice are abolished in KOR knock-out mice. Finally, we have received a single anecdotal report that the profound actions of salvinorin A on human consciousness and perception are abolished by naloxone (Sheffler and Roth, 2003). Hence, centrally active KOR agonists are not likely to be effective medications in humans because of CNS side-effects. Taken together, these studies support our proposal that salvinorin A exerts its actions in humans via activation of KORs, although more research is needed to verify this hypothesis.

Conclusion

The frequently abused hallucinogen salvinorin A represents the most potent, selective and efficacious KOR known. Salvinorin A induces spatiotemporal dislocation in humans—an effect likely mediated by KOR agonism. A detailed study of salvinorin A's mode of action will likely help to illuminate the role of the kappergic system in human brain function.

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