

Salvinorin A, an Active Component of the Hallucinogenic Sage *Salvia divinorum*, is a Highly Efficacious Kappa Opioid Receptor Agonist: Structural and Functional Considerations antagonist in the treatment of opioid dependence

by

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ABSTRACT

The diterpene salvinorin A from *Salvia divinorum* has recently been reported to be a high affinity and selective kappa-opioid receptor agonist (Roth et al, 2002). Salvinorin A and selected derivatives were found to be potent and efficacious agonists in several measures of agonist activity using cloned human kappa-opioid receptors expressed in HEK-293 cells. Thus, salvinorin A, salvinorinyl-2-propionate and salvinorinyl-2-heptanoate were found to be either full (salvinorin A) or partial (2-propionate; 2-heptanoate) agonists for inhibition of forskolin-stimulated cAMP production. Additional studies of agonist potency and efficacy of salvinorin A, performed by co-transfecting either the chimeric G proteins Gaq-i5 or the universal G protein Ga16 and quantification of agonist-evoked intracellular calcium mobilization, affirmed that Salvinorin A was a potent and effective kappa-opioid agonist. Results from structure-function studies suggested that the nature of the substituent at the 2 position of salvinorin A was critical for kappa-opioid receptor binding and activation. Since issues of receptor reserve complicate estimates of agonist efficacy and potency, we also examined the agonist actions of salvinorin A by measuring potassium conductance through G protein gated K(+) channels co-expressed in *Xenopus* oocytes-system in which receptor reserve is minimal. Salvinorin A was found to be a full agonist, being significantly more efficacious than U50488 or U69593 (two standard kappa-opioid agonists) and similar in efficacy to dynorphin A (the naturally occurring peptide ligand for kappa-opioid receptors). Salvinorin A thus represents the first known naturally-occurring non-nitrogenous full agonist at kappa-opioid receptors.

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