

A Review of the Properties of Spiradoline: A Potent and Selective κ -Opioid Receptor Agonist

M-L. G. Wadenberg

*Departments of Physiology & Pharmacology, Section for Neuropsychopharmacology,
Karolinska Institutet, Stockholm, Sweden*

Key words: Analgesics—Antitussives—Dopamine receptors—Dopamine-opioid interaction— κ -Opioid agonists—Neuroprotection—Opioids—Spiradoline— U62,066E—U50488H.

ABSTRACT

The selective κ -opioid receptor agonist spiradoline mesylate (U62,066E), an arylacetamide, was synthesized with the intention of creating an analgesic that, while still retaining its analgesic properties, would be devoid of the, mainly μ receptor mediated, side effects such as physical dependence and respiratory depression associated with morphine. Spiradoline is highly selective for the κ receptor with K_i of 8.6 nM in guinea pig. Examination of the enantiomers of spiradoline, showed the (–)enantiomer to be responsible for the κ agonist properties. Spiradoline easily penetrates the blood brain barrier, and does not seem to have any significant active metabolites. In preclinical studies, spiradoline has a short duration of action with a peak at around 30 min after administration.

The analgesic properties of spiradoline are well documented in mice and rats. Antitussive properties have also been reported in rats. Furthermore, spiradoline was reported to display effects suggestive of neuroprotective properties in animal models of ischemia. In humans, spiradoline is a potent diuretic. It also produces significant sedation presumably due to its antihistamine properties. Preclinical studies have shown that spiradoline reduces blood pressure and heart rate, and has possible antiarrhythmic properties. Clinical studies did not confirm these findings.

κ Receptors inhibit dopaminergic neurotransmission. Spiradoline, given systematically to rats, produces a significant and long lasting decrease in dopamine release, and in locomotor activity. It has also antipsychotic-like effect in animal behavioral tests. At low doses spiradoline was reported to decrease tics in patients with Tourette's syndrome. Although spiradoline had promising effects in animal tests of analgesia, and a reasonably good safety profile in preliminary studies, it did not replace morphine as an analgesic. The available clinical data suggest that spiradoline produces disturbing adverse effects such as diuresis, sedation, and dysphoria at doses lower than those needed for analgesic effects. Thus, future development of spiradoline-like analgesic compounds should preferably focus on reduction of unwanted effects on the central nervous system.

Spiradoline, which currently is commercially available for preclinical research, might prove useful in some psychiatric conditions and possibly as a neuroprotective agent.