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RX 821002 as a Tool for Physiological Investigation of α_2-Adrenoceptors

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ABSTRACT

RX 821002 is the 2-methoxy congener of idazoxan. In binding and tissue studies it behaves as a selective antagonist of α_2-adrenoceptors, with at least 5 times greater affinity for these receptors than any other binding site. It does not select between the different types of α_2-receptor. Although this drug probably has no future as a therapeutic agent, it remains a good probe for physiological activity at α_2-adrenoceptors in animal experiments. A particularly useful feature of this compound is its lack of binding at I_1 and I_2 imidazoline receptors. However, it has relatively high affinity for 5-HT_{1A} receptors (at which it acts as an antagonist) and a tendency to behave as an inverse agonist at α_{2A}-adrenoceptors in some cell culture systems. These potential drawbacks may be overcome by careful design of experiments, and the greater selectivity of RX 821002 renders it much superior to yohimbine or idazoxan as a tool for probing physiological actions at α_2-receptors. It can be compared favorably with other selective antagonists such as atipamezole.

In physiological studies, RX 821002 augments norepinephrine release in the frontal cortex and increases drinking behavior in rat. In rabbit, intrathecal administration of this drug enhances somatic and autonomic motor outflows, showing that tonic adrenergic descending inhibition of withdrawal reflexes and sympathetic pre-ganglionic neurons is strong in this species. The potentiation of reflexes may be considered a pro-nociceptive action. In the same model, RX 821002 antagonizes the inhibitory effects of the μ opioid fentanyl, indicating that exogenous opioids synergize with endogenously released norepinephrine in the spinal cord. Thus, the careful use of RX 821002 has revealed several aspects of the physiological activity of α_2-adrenoceptors in rabbit spinal cord and rat brain. We recommend that RX 821002 and/or compounds with similar selectivity for α_2-adrenoceptors (atipamezole, MK-912, RS-79948) should be used in preference to yohimbine or idazoxan in all future studies of this type.