INTRODUCTION

- Monoamines are major targets for currently available antidepressant drugs, particularly those inhibiting the reuptake of serotonin (5-HT) and/or norepinephrine (NE).

- Multiple sources of evidence suggest that dopamine (DA) is also involved in the pathophysiology of mood disorders. In particular, it has been reported that the prevalence of depression can reach up to 50% of individuals suffering from Parkinson’s disease. Conversely, it is possible to achieve an antidepressant response by enhancing DA neurotransmission.

- SEP 225289 is a 5-HT, NE and dopamine (DA) reuptake inhibitor. It belongs to a new class of antidepressant drugs whose preclinical antidepressant-like activity has been repeatedly reported (Table 1).

- The purpose of the present study was to examine the electrophysiological effects of SEP 225289 on the firing activity of monoaminergic neurons and characterize its mechanism of action.

MATERIAL AND METHODS

- Electrophysiological experiments were carried out in Sprague Dawley rats weighing 250-300g. Rats were anaesthetized with chloral hydrate (400 mg/kg; ip) and mounted in a stereotaxic apparatus (David Kopf Instruments). The extracellular recordings were carried out using single-glas micropipettes in the dorsal raphe nucleus (DRN), the locus coeruleus (LC) and the ventral tegmental area (VTA) and with multi-barreled glass pipettes in the CA3 of the hippocampus.

- Extracellular unitary recordings in the DRN, LC and VTA: single electrodes (4-7 Mohm) were positioned using the following coordinates (in mm from bregma): AP, -3.8, L, 4; V, 3. Stimulated quisqualate pyramidal neurons were identified according to their typical characteristics -3.8, L, 4; V, 3. Presumed 5-HT, NE and VTA neurons were then identified using the criteria previously described by Aghajanian and Vandermaelen, 1982; Grace and Bunney, 1983. The predominant inhibitory effect of SEP 225289 was detected in the LC while it produced only a partial decrease in VTA DA and DRN 5-HT neuronal activities. The unexpected moderate inhibitory effect of SEP 225289 in the DRN is not due to a lesser degree of reuptake blockade of 5-HT than for NE because it is similarly effective in prolonging the recovery of firing of pyramidal neurons thereby limiting the inhibitory effect of SEP 225289 in the DRN. The observation that SEP 225289 activates the firing of 5-HT neurons in the presence of the 5-HT1A receptor antagonist WAY 100635 is consistent with this hypothesis.

RESULTS WITH SEP 225289

1- Comparison of the effects of the SEP 225289 on the firing activity of LC NE, VTA DA and DR 5-HT neurons

- Figure 1. A, B, C: examples of integrated firing histograms showing the effect of cumulative doses of SEP 225289 on the spontaneous activity of LC NE, VTA DA and DRN 5-HT neurons. B and C: means ± SEM of percent of increase in basal firing rate observed at each dose in the DRN (n = 7), VTA (n = 7) and DRN (n = 10).

2- In vivo potency of SEP 225289 for 5-HT and NE transporters in the hippocampus

- Figure 2. A: examples of integrated firing histograms showing the effect of microiontophoretically-applied 5-HT and NE before and following cumulative doses of SEP 225289 in the DRN 5-HT neuronal activity. B, C: means ± SEM of percent of increase or decrease in basal firing rate observed at each dose in the DRN (n = 7), VTA (n = 7) and DRN (n = 10).

3- Effect of 5-HT1A receptor antagonism on the electrophysiological action of SEP 225289 on DR 5-HT firing rate

- SEP 225289 reduced the firing rate of NE, DA and 5-HT neurons through the activation of 5-HT1A autoreceptors, respectively. The predominant inhibitory effect of SEP 225289 was detected in the LC while it produces only a partial decrease in VTA DA and DRN 5-HT neuronal activities. The unexpected moderate inhibitory effect of SEP 225289 in the DRN is not due to a lesser degree of reuptake blockade of 5-HT than for NE because it is similarly effective in prolonging the recovery of firing of pyramidal neurons thereby limiting the inhibitory effect of SEP 225289 in the DRN. The observation that SEP 225289 activates the firing of 5-HT neurons in the presence of the 5-HT1A receptor antagonist WAY 100635 is consistent with this hypothesis.

REFERENCES


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CONCLUSIONS / DISCUSSION

SEP 225289 reduced the firing rate of NE, DA and 5-HT neurons through the activation of 5-HT1A autoreceptors, respectively. The predominant inhibitory effect of SEP 225289 was detected in the LC while it produces only a partial decrease in VTA DA and DRN 5-HT neuronal activities. The unexpected moderate inhibitory effect of SEP 225289 in the DRN is not due to a lesser degree of reuptake blockade of 5-HT than for NE because it is similarly effective in prolonging the recovery of firing of pyramidal neurons following 5-HT and NE applications. It is thus possible that noradrenergic and/or dopaminergic inputs innervating the DRN produce excitatory influence on 5-HT neurons thereby limiting the inhibitory effect of SEP 225289 in the DRN. The observation that SEP 225289 activates the firing of 5-HT neurons in the presence of the 5-HT1A receptor antagonist WAY 100635 is consistent with this hypothesis.