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J. Pharm. Pharmacol. 1981, 33: 187–188
Communicated November 5, 1980

0022–3573/81/030187–02 $02.50/0

α_2-Adrenoceptor-blocking action of the phenylethanolamine-*N*-methyltransferase inhibitor SKF 64139

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7,8-Dichloro-1,2,3,4-tetrahydroisoquinoline (SKF 64139) is an inhibitor of phenylethanolamine-*N*-methyltransferase (PNMT–Pendleton et al 1976). When administered to rats, it induced the depletion of adrenaline from the dorsal midline area of the caudal medulla oblongata, and this effect was significantly reduced by clonidine (Fuxe et al 1979). In addition to its ability to inhibit PNMT, SKF 64139 is a weak, but specific, antagonist at the postsynaptic α_1-adrenoceptors in rabbit aorta ($pA_2 = 5{\cdot}2$; Pendleton et al 1976). In view of this observation it seemed possible that SKF 64139 might also be an antagonist at presynaptic α_2-adrenoceptors. The experiments now reported were carried out to investigate this possibility.

The pA_2 for SKF 64139 against noradrenaline (Koch-Light) at post-synaptic α_1-adrenoceptors in rabbit isolated aorta was determined as described by Apperley et al (1976). The pA_2 for SKF 64139 against clonidine (Boehringer) at presynaptic α_2-adrenoceptors in the guinea-pig isolated ileum was determined using the method described by Drew (1978).

SKF 64139 (10^{-5}, 3×10^{-5} and 10^{-4} M) caused concentration-dependent, parallel, rightward displacements of the concentration-response curve to noradrenaline in the rabbit aorta without causing any reduction in the maximum response to noradrenaline. Similarly SKF 64139 (10^{-6}, 3×10^{-6} and 10^{-5} M) antagonized the clonidine-induced inhibition of the twitch response to field stimulation of the guinea-pig ileum, although it was rather more potent an antagonist in this tissue. SKF 64139, itself, had little or no effect on the twitch response and did not reduce the maximal response to clonidine. The mean pA_2 values for SKF 64139 at α_1- and α_2-adrenoceptors, and the mean slopes of the Schild plots from which they are derived, are shown in Table 1. It can be seen that SKF 64139 is approximately twenty times more potent at blocking effects mediated via α_2- than via α_1-adrenoceptors in vitro. The α_1:α_2 potency is similar to that found for yohimbine (Doxey et al 1977), but SKF 64139 is approximately 10 times less potent than yohimbine.

Table 1. The α-adrenoceptor-blocking potencies of SKF 64139. Results are expressed as mean (and 95% confidence limits). Slope = Slope of regression of log (agonist dose-ratio-1) vs log molar concentration of antagonist (Arunlakshana & Schild 1959).

	Postsynaptic α_1-adrenoceptors (rabbit aorta) (n = 6)	Presynaptic α_2-adrenoceptors (guinea-pig ileum) (n = 7)
pA_2	5·47 (5·24–5·70)	6·79 (6·60–6·98)
Slope	0·98 (0·88–1·08)	1·17 (1·03–1·31)

n = Number of experiments.

In view of its relatively high potency in blocking α_2-adrenoceptors it is possible that this effect of SKF 64139 will occur at plasma concentrations shown to inhibit PNMT (Pendleton et al 1976). Thus, caution should be exercised when interpreting the interaction between SKF 64139 and α-adrenoceptor agonists, or the effects of SKF 64139 on adrenaline turnover, since presynaptic α_2-adrenoceptor blockade or PNMT inhibition could produce similar effects. For example, either effect of SKF 64139 could lead to a clonidine-sensitive increase in adrenaline turnover (Scatton et al 1979). In the central nervous system some α_2-adrenoceptors, such as those in the locus coeruleus, are located postsynaptically (Cedarbaum & Aghajanian 1977) and may receive an inhibitory adrenergic input; the SKF 64139-induced acceleration in the firing rate of locus coeruleus units observed by Svensson & Engberg (1980) could be due either to its PNMT-inhibitory activity or to blockade of these postsynaptic α_2-adrenoceptors. Other PNMT inhibitors related to SKF 64139 should be investigated for their α-adrenoceptor-blocking properties.

The author gratefully acknowledges Mr D. Baker and Mr I. Weston for excellent technical assistance and Dr R. G. Pendleton for the supply of SKF 64139.

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J. Pharm. Pharmacol. 1981, 33: 188–189
Communicated August 26, 1980

0022–3573/81/030188–02 $02.50/0

The inhibitory effect of paracetamol on the electrically stimulated ileum of the guinea-pig

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Prostaglandin synthetase inhibitors have been reported to inhibit the electrically-evoked contractions of the guinea-pig ileum (Bennett et al 1975). The depressant effect of these drugs is rapidly negated by the addition to the organ bath of prostaglandins E_1 or E_2 (Sokunbi 1979). These findings have led to the suggestion that prostaglandins facilitate cholinergic transmission in this tissue.

In contrast to many peripherally acting analgesics, paracetamol is devoid of anti-inflammatory activity but it has been reported to inhibit prostaglandin synthetase at concentrations ranging from 92 μM–3·9 mM. The ability of paracetamol to inhibit prostaglandin synthetase varies with the tissue being examined; one of the most sensitive is the rabbit brain where paracetamol has an IC50 of 92 μM (Flower & Vane 1974).

We have measured the effect of paracetamol on the guinea-pig electrically-stimulated myenteric plexus-longitudinal muscle preparation (MPLM).

The MPLM was prepared as described by Paton & Zar (1968) and suspended in a 5 cm^3 bath containing Krebs' solution gassed with 95% oxygen and 5% carbon dioxide. Contractions were recorded isotonically under a tension of 0·3 g. Tissues were stimulated through ring electrodes at supramaximal voltage with 1 ms pulses at a frequency of 0·1 Hz. The mouse field stimulated vas deferens preparation was as described by Shaw & Turnbull (1978).

Paracetamol, at concentrations ranging from 10–400 μM produced a dose-dependent inhibition of the electrically evoked contractions of the MPLM (Fig. 1) which was readily removed by washing. However, the inhibitory effect of aspirin, produced over the same range of concentration, persisted even after repeated washing.

In agreement with Sokunbi (1979) that the inhibitory effects of PG synthetase inhibitors are removed by the addition of prostaglandins, we found that paracetamol inhibition was readily negated by PGE_1 2 ng ml^{-1} Fig. 2).

Ehrenpreis et al (1973) have reported that the inhibitory effect of morphine on this tissue is also negated by PGE_1 and PGE_2 at concentrations similar to those we used. We have confirmed the ability of PGE_1 (2 ng ml^{-1}) to negate the inhibitory effect of morphine on the MPLM.

However, the depressant effect of paracetamol and aspirin seen on the MPLM is unlikely to be mediated

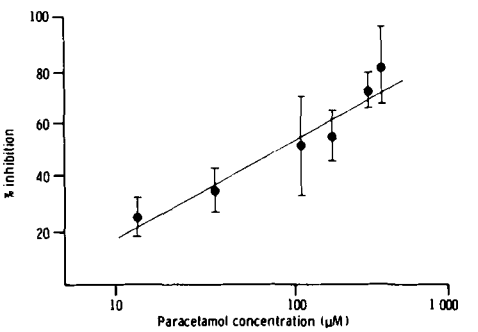

FIG. 1. Dose-response relationship for paracetamol on guinea-pig ileum myenteric plexus-longitudinal muscle preparation. The regression line was calculated from a total of 15 observations.

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