Contraction of the rat isolated colon by adrenaline

After β-adrenoceptor blockade with oxprenolol, adrenaline or noradrenaline contracted the rat isolated colon, and also human and rabbit taeniae coli (Gagnon, 1970; Gagnon & Belisle, 1970; Belisle & Gagnon, 1971). We now report the effect of two new β-adrenoceptor blocking agents, MK 950* and alprenolol, on the action of adrenaline on rat isolated colon.

A segment of 3 to 4 cm of rat ascending colon was mounted in an organ bath and immediately superfused with Krebs solution (Gaddum, 1953, and see Belisle & Gagnon, 1971). Changes in the base-line were calculated with a Keuffel & Esser planimeter and expressed as the area (cm^2) below the tracing. The concentrations of drugs are calculated as free bases.

After control responses (relaxations) to increasing doses (3, 10, 30 and 100 ng/ml) of adrenaline, the agonist was tested in the presence of one of the β-adrenoceptor blocking agents, added 15 min before. Our aim was to find a dose of the blocking agents which, as with oxprenolol, would not only prevent the relaxing action of all doses of adrenaline but would transform this response into dose-dependent contractions. Fig. 1 shows that after doses of 10 and 25 μg/ml of MK 950, adrenaline, especially in higher concentrations, induced contractions that were not dose-dependent Apparently, the large doses of adrenaline could partially overcome the blockade of β-adrenoceptors by MK 950.

However, after a larger dose (50 μg/ml) of MK 950, adrenaline elicited a contractile response which was dose-related. As can be seen in Fig. 1, alprenolol influenced the responses of the rat colon to adrenaline similarly.

It is evident that both MK 950 and alprenolol, like oxprenolol, can unmask excitatory responses in intestinal smooth muscle exposed to adrenaline. These three agents differ from propranolol after which, dose-dependent contractions of the preparation could not be obtained in response to adrenaline; this can be explained by the fact that propranolol fulfils the conditions of competitive antagonism to sympathomimetic amines at the α-adrenoceptor sites (Gulati, Gokhale & others, 1968). In the current experiments, we did not attempt to characterize the contractile responses to adrenaline after MK 950 and alprenolol.

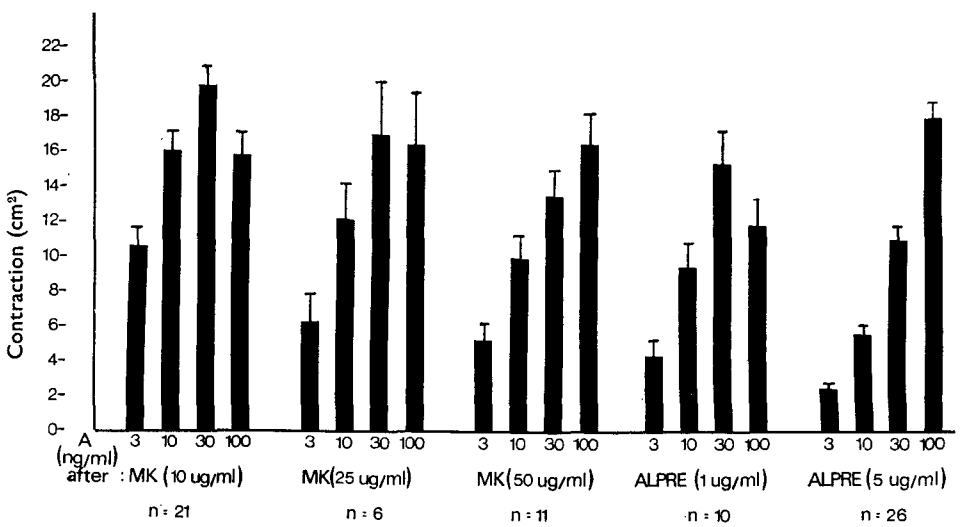

FIG. 1. Contractile effects of adrenaline upon the rat isolated colon preparation after β-adrenergic blockade with increasing doses of MK 950 and alprenolol. A = Adrenaline, MK = MK950, ALPRE = Alprenolol, n = number of observations.

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* S-(−)-3-(3-t-Butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole maleate.

Effects of caffeine on central monoamine neurons

There is strong evidence that cyclic adenosine-3′,5′-monophosphate (cyclic AMP) plays an important regulating role in the function of the nervous system (see book edited by Greengard & Costa, 1970). The data so far support both a presynaptic and a postsynaptic action of cyclic AMP in synaptic transmission (Breekenridge & Bray, 1970; Hoffer, Siggins & Bloom, 1970). In line with this view it has been found that caffeine and theophylline, which are known to inhibit the catabolic enzyme cyclic 3′,5′-nucleotide phosphodiesterase (Butcher & Sutherland, 1962), can release noradrenaline in the mammalian brain (Berkowitz, Tarver & Spector, 1970). On the other hand, it has recently been pointed out that methylxanthines fail to augment cyclic AMP concentrations in brain (Sattin, 1971). Therefore the pharmacological effects of these compounds may not necessarily be mediated via inhibition of the phosphodiesterase (Rall & Sattin, 1970). The present paper confirms the results of Berkowitz & others (1970) and provides evidence for the view that methylxanthines can cause an increase in noradrenaline turnover, but a decrease of 5-hydroxytryptamine (5-HT) and particularly of dopamine turnover.

Male Sprague-Dawley rats (150–200 g) in groups of 4–8 were used. Dopamine, noradrenaline and 5-HT turnover were evaluated by examining the decline of the amine stores after treatment with the tyrosine hydroxylase inhibitor, α-methyl-*p*-tyrosine methylester (H44/68) and the tryptophan hydroxylase inhibitor α-propyldopacetamide (H22/54) (see review by Andén, Corrodi & Fuxe, 1969). Both biochemical and histochemical amine analysis were made (Bertler, Carlsson & Rosengren, 1958; Carlsson & Waldeck, 1958; Carlsson & Lindqvist, 1962; Bertler, 1961; Falck, Hillarp & others, 1962; Corrodi & Jonsson, 1967). Caffeine citrate was given (i.p.) 15 min before the injection of H44/68 (250 mg/kg, i.p.) or of H22/54 (500 mg/kg, i.p.) 4 and 3 h before animals were killed, respectively. All the doses used refer to the base. Histochemically, the effects of aminophylline (theophylline ethylenediamine, 200 mg/kg, i.p.) were studied on the H44/68-induced disappearance of catecholamine fluorescence and on the H22/54-induced disappearance of 5-HT fluorescence. Aminophylline was given 1 h before the inhibitor.

The effects of caffeine administered *in vitro* (10^{-5} or 10^{-4}M) or *in vivo* (100 mg/kg, i.p., 2 h) on the *in vitro* uptake and retention of [^{3}H]noradrenaline (^{3}H-NA) (10^{-7}M) or ^{14}C-5-HT (10^{-6}M) in slices from the neostriatum and the cerebral cortex have also