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Study on the histamine-like activity of guanfacine

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Abstract—The effects of guanfacine have been studied on guinea-pig isolated atria and diethylstilboestrol-treated rat isolated uterus to determine whether it possesses histamine-like activity. Guanfacine produced a concentration-dependent negative chronotropic effect which was not modified by ranitidine (0·1 μM). In rat isolated uterus contracted by KCl, clonidine (5–5000 μM) produced concentration-dependent relaxation which was blocked by ranitidine (0·1 μM), but guanfacine only produced relaxation at high concentrations (100–1000 μM), and this was not affected by ranitidine (0·1 μM). It is concluded that guanfacine, unlike clonidine, does not produce effects due to activation of H_2-receptors in either guinea-pig atria or rat uterus.

Some α-adrenoceptor agonists of the clonidine type possess histamine-like activity in addition to acting on α-adrenoceptors (Medgett & McCulloch 1979; Kenakin & Angus 1981; Ganellin 1982). Recently, the lack of histamine-like activity of rilmenidine has been shown, and the absence of this property has been implicated in the lack of a sedative effect (Li & Rand 1989).

Guanfacine is a non-imidazoline antihypertensive agent with a mechanism of action similar to both clonidine and rilmenidine and, like clonidine, it also produces sedation (Reid et al 1983; Timmermans 1984). Since guanfacine differs in molecular structure from both clonidine and rilmenidine, experiments were carried out to determine whether it possesses histamine-like activity.

Materials and methods

Adult guinea-pigs, 350–450 g, were stunned by a blow on the head and exanguinated. The heart was rapidly removed and the right atria was dissected free and mounted in a 20 mL organ-bath containing Krebs-Henseleit solution at 37 °C, of the following composition (mM): NaCl 118, KCl 4·7, $NaHCO_3$ 25, $MgSO_4$ 0·45, KH_2PO_4 1·03, $CaCl_2$ 2·5, D-(+)-glucose 11·1, aerated with 5% CO_2 in O_2. The spontaneous atrial contractions were measured with an isometric strain gauge exerting a diastolic tension of 1 g, and their force and rate were continually recorded on a multichannel HP 7788 A polygraph. The preparation was allowed to equilibrate for at least 30 min before cumulative concentration-response curves to guanfacine in the absence or presence of ranitidine were obtained.

Female Wistar rats, 200–250 g, were treated with diethylstilboestrol (5 mg kg^{-1}, i.p.) 24 h before they were stunned by a blow to the head and exanguinated. The uterine horns were mounted in a 20 mL organ-bath containing De Jalon Solution at 31 °C, of the following composition (mM): NaCl 154, KCl 5·6, $CaCl_2$ 0·4, $NaHCO_3$ 5·95 and D-(+)-glucose 2·5, aerated with 5% CO_2 in O_2. The tissue was attached to an isotonic transducer Ugo Basile (mod Gemini 7070). After equilibration for 30 min under a resting tension of 1 g, a submaximal well-maintained plateau contraction was obtained by adding KCl 37 mM, and then cumulative concentration-response curves to guanfacine and clonidine in the absence and presence of different antagonists (ranitidine, yohimbine, propranolol and atropine) were obtained. Antagonists were incubated for 15 min.

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On guinea-pig atria the response to guanfacine was expressed as the percentage change from the baseline values. The responses to agonists in rat isolated uterus were expressed as the percentage-inhibition of the KCl-induced contraction. Effective concentration 50% (EC50) was calculated graphically from a plot of log concentrations vs percentage response produced by each agonist in individual experiments. All data are shown as mean ± standard error of the mean (s.e.m.). Statistical analysis of the data was carried out using Student's *t*-test at a 5% significance level.

The drugs used were: guanfacine and clonidine, generously supplied by Sandoz SAE and Boehringer Ingelheim SA, respectively. Atropine, ranitidine, propranolol and yohimbine were from Sigma Co.

Results

Guanfacine (0·01 1000 μM) produced a concentration-dependent decrease in the atrial rate. The maximal response to guanfacine on the atrial rate was not reached, even with the highest concentration used. Ranitidine (0·1 μM) did not modify the negative chronotropic effect of guanfacine (Fig. 1). The force of contraction was also decreased by guanfacine ($-19·1 \pm 4·1\%$; $n = 6$).

Clonidine (5–5000 μM) produced a concentration-dependent inhibition of KCl-induced contractions of the isolated rat uterus, but guanfacine inhibited the contractions only at concentrations above 100 μM. The maximum effect for both agonists was similar ($98·7 \pm 1·3\%$ and $98·3 \pm 1·1\%$, respectively) and was achieved at concentrations of 1500 and 1000 μM, respectively. Ranitidine (0·1 μM) failed to modify the relaxation produced by guanfacine, but produced a parallel shift to the right of the concentration-response curve for clonidine without any modification of the maximal effect ($99·0 \pm 2·5\%$). Propranolol (0·1 μM), yohimbine (0·1 μM) and atropine (0·001 μM) did not modify the guanfacine-induced relaxation of the KCl-contracted rat uterus (Table 1).

Discussion

Clonidine has previously been shown to activate histamine H_2-receptors in both isolated guinea-pig atria (Parsons 1978; Medgett & McCulloch 1979; Rubio et al 1982) and isolated rat

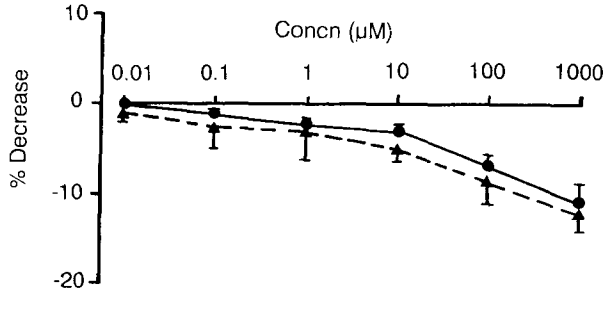

FIG 1. Concentration-response curve for the chronotropic effects of guanfacine on guinea-pig isolated atria, in the absence (●) and presence (▲) of ranitidine (0·1 μM). Symbols indicate mean values and standard error of the mean with $n = 6$ for each point.

Table 1. EC50 values for clonidine and guanfacine alone and after various pretreatments in the isolated uterus of diethylstilboestrol-treated rats.

Agonist	Pretreatment	EC50 (μM)	n
Clonidine	—	76·0 ± 10·0	6
Clonidine	Ranitidine (0·1 μM)	1010·0 ± 200·0	6
Guanfacine	—	194·0 ± 20·0	29
Guanfacine	Ranitidine (0·1 μM)	140·0 ± 40·0	8
Guanfacine	Yohimbine (0·1 μM)	120·0 ± 40·0	7
Guanfacine	Propranolol (0·1 μM)	210·0 ± 40·0	7
Guanfacine	Atropine (0·001 μM)	185·0 ± 30·0	7

n = the number of experiments.

uterus (Goyal et al 1983; Rubio et al 1984; Li & Rand 1989). Histamine-like activity is also shown by some related α-adrenoceptor agonists (Medgett & McCulloch 1978; McCulloch et al 1980). In contrast, rilmenidine, a non-imidazoline derivative, failed to exhibit histamine-activity (Li & Rand 1989). Similarly, the present results show that guanfacine has no histamine-like activity in rat isolated uterus and guinea-pig atria, confirming previous results on gastric secretion (Medgett & McCulloch 1979). Furthermore, guanfacine, like rilmenidine, produced a negative chronotropic effect that was not modified by ranitidine. Li & Rand (1989), suggested that the negative chronotropic effect of rilmenidine may be due to activation of potassium channels; our results with guanfacine could be explained in the same way.

Moreover, guanfacine at the highest concentration used produced a relaxant effect on the uterus which was not due to H_2-histamine receptor activation. This effect of guanfacine was not affected by drugs that block α- or β-adrenoceptors and muscarinic receptors. The involvement of noradrenergic and cholinergic receptors or the release of endogenous catecholamines could be excluded. These findings are in agreement with those obtained with rilmenidine in isolated guinea-pig atria (Li & Rand 1989).

It has been suggested that rilmenidine does not produce sedation because of the lack of histamine-like activity. The results with guanfacine in the present investigation failed to support the above suggestion, although some differences in pharmacological activity between clonidine-like compounds may be reflected in differences between their clinical effects.

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