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EFFECTS OF IMPROMIDINE, A SPECIFIC H_2-RECEPTOR AGONIST AND 2-(2-PYRIDYL)-ETHYLAMINE, AN H_1-RECEPTOR AGONIST, ON STIMULATION-INDUCED RELEASE OF [^{3}H]-NORADRENALINE IN GUINEA-PIG ISOLATED ATRIA

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1 The specific histamine H_2-receptor agonist, impromidine (3–100 nmol/l), increased the rate and force of beating of guinea-pig isolated atria. These effects were blocked by the H_2-receptor antagonist, cimetidine (30 μmol/l), but not by the H_1-receptor antagonist, mepyramine (0.1 μmol/l).

2 In atria that had previously been incubated in [^{3}H]-noradrenaline, impromidine (3–100 nmol/l) had no effect on the resting efflux of radioactivity, but concentrations of 50 and 100 nmol/l significantly increased the efflux induced by electrical stimulation (2 Hz for 10 s) of the intramural sympathetic nerves by approximately 38%; lower concentrations (3, 10 and 25 nmol/l) had no effect.

3 The effect of impromidine in enhancing stimulation-induced efflux of radioactivity was abolished by cimetidine (30 μmol/l) and by mepyramine (0.1 μmol/l). It was unaffected by the α-adrenoceptor antagonist, phentolamine (30 μmol/l).

4 Impromidine produced some inhibition of the uptake of [^{3}H]-noradrenaline, but this did not account for the enhancement of the stimulation-induced efflux of radioactivity, since impromidine (50 nmol/l) still increased release in the presence of cocaine (30 μmol/l).

5 The specific H_1-receptor agonist, 2-(2-pyridyl)-ethylamine (10–100 μmol/l), increased both the resting and stimulation-induced efflux of radioactivity. These effects were not blocked by mepyramine (0.1 μmol/l) or the β-adrenoceptor antagonist, metoprolol (0.1 μmol/l).

6 The prejunctional inhibitory histamine receptors in guinea-pig atria are not classifiable into H_1- or H_2-type by the use of relatively specific postjunctional histamine H_1- or H_2-receptor agonists and antagonists.

Introduction

Transmitter release from sympathetic noradrenergic nerves can be modulated by a number of drugs that act on receptors that are located prejunctionally (Starke, 1977; Westfall, 1977). Of the autacoids, histamine has been shown to have a prejunctional inhibitory action on sympathetic neuroeffector transmission in the heart (Lokhandwala, 1978), blood vessel strips (McGrath & Shepherd, 1976), the perfused gracilis muscle (Powell, 1979) of the dog, and in guinea-pig isolated atria (Wong-Dusting, Medgett, Rand & Story, 1979; Rand, Story & Wong-Dusting, 1982).

In the canine heart, blood vessel strips and gracilis muscle, histamine inhibited responses to sympathetic nerve stimulation, but did not affect the responses to exogenous noradrenaline (McGrath & Shepherd, 1976; Lokhandwala, 1978; Powell, 1979), thus indicating a prejunctional site of action. In the canine heart and blood vessels the prejunctional histamine receptors involved appear to be of the H_2-subtype, since the effects of histamine were blocked by the H_2-receptor antagonist, metiamide, but not by the H_1-receptor antagonist, mepyramine. In the canine perfused gracilis muscle, the inhibitory effects of histamine were blocked by both mepyramine and the H_2-receptor antagonist, metiamide; however, Powell (1979) considered the prejunctional receptors involved were also of the H_2-type, as the specific H_2-receptor agonist, dimaprit, mimicked the action of histamine. In guinea-pig isolated atria in which transmitter stores had been labelled with [^{3}H]-noradrenaline, there was a decreased release of radioactivity in the presence of histamine and this effect was blocked by mepyramine and by the H_2-receptor antagonist, cimetidine (Wong-Dusting *et al.*, 1979; Rand *et al.*, 1982), but it was suggested that the histamine receptors involved were probably of the H_2-type as the concentration of mepyramine used was high. This paper deals with a further attempt to characterize the prejunctional histamine receptors of

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noradrenergic terminals in guinea-pig atria by using the highly specific and potent postjunctional H_2-receptor agonist, impromidine (Durant, Duncan, Ganellin, Parsons, Blakemore & Rasmussen, 1978) and the relatively specific H_1-receptor agonist, 2-(2-pyridyl)-ethylamine (Durant, Ganellin & Parsons, 1975).

Methods

Guinea-pigs of either sex (300–500 g) were stunned by a blow to the head and exsanguinated. The hearts were rapidly removed and the atria were dissected free and mounted in an organ bath containing 2.5 ml of Krebs-Henseleit solution of the following composition (mmol/l): 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 and disodium edetate 0.065. The solution in the organ bath and in the reservoirs supplying the organ bath was gassed with a mixture of 95% O_2 in CO_2 and maintained at a temperature of 37°C. The force and rate of spontaneous atrial contractions were recorded either on a Brush 250 or a Grass 79D pen recorder using a high-compliance strain gauge transducer: the basal tension was adjusted to about 10 mN. After an equilibration period of 60 min, the atria were incubated with [^{3}H]-noradrenaline (4 μCi/ml, 0.38 to 0.4 μmol/l) for 20 min. The solution in the organ bath was then repeatedly exchanged with noradrenaline-free Krebs-Henseleit solution for 60 min to remove loosely bound tritiated compounds.

The atrial intramural nerves were electrically stimulated through platinum wire electrodes with monophasic square waves of 1 ms duration and supramaximal voltage. In each experiment, two periods of field stimulation consisting of 20 pulses at a frequency of 2 Hz were given 22 min apart. Atropine (0.3 μmol/l) was present in the Krebs-Henseleit solution throughout the experiment to block responses to stimulation of cholinergic nerves. The efflux of radioactivity into the bathing solution was measured in collections of the bathing fluid taken after 1 min contact periods with the atria. For each period of stimulation, six consecutive collections of the bathing solution were taken, starting 3 min before stimulation. The resting efflux of radioactivity (d/min) preceding each period of stimulation was calculated as the mean amount of radioactivity present in the three 1 min pre-stimulation collections of bathing solution. The stimulation-induced efflux of radioactivity was calculated by subtracting the resting efflux of radioactivity from the amounts of radioactivity in each of the three 1 min collections taken during and after electrical stimulation was applied, and summing the differences.

The effects of the histamine receptor agonists, impromidine and 2-(2-pyridyl)-ethylamine, on the resting and stimulation-induced efflux of radioactivity were investigated by adding the test agonist to the bathing solution at least 15 min before the second period of stimulation; it was then present for the remainder of the experiment. In experiments designed to assess the effects of impromidine in the presence of another drug, the latter drug was added 30 min before the first stimulation period and was present for the remainder of the experiment.

In each experiment, resting and stimulation-induced effluxes in the second period of stimulation were expressed as percentages of the corresponding effluxes during the first periods. This procedure takes account of variation between tissues in the absolute amounts of radioactivity released; furthermore, statistical comparison with a matching set of control preparations takes account of changes in resting and stimulation-induced effluxes due to time alone (McCulloch, Rand & Story, 1974; Hope, McCulloch, Rand & Story, 1978).

For the determination of radioactivity, 1 ml aliquots of the collections of the bathing solution were added to the scintillation vials, together with 0.2 ml of 6 mol/l HCl and 10 ml of a liquid scintillation solution of the following composition: 5.5 g of 2,5-diphenyloxazole (PPO), 0.1 g of 1,4-bis-2-(5-phenyloxazolyl)-benzene (POPOP) and 333 ml of Triton X made up to 1 litre with toluene. The radioactivity was measured in a Packard model 3330 or 3380 liquid scintillation spectrometer.

To measure the uptake of noradrenaline, isolated atria were incubated for 10 min with [^{3}H]-noradrenaline (4 μCi/ml; 0.4 μmol/l). After incubation, the atria were removed from the organ bath, blotted, weighed and homogenized in 1.5 ml of 0.4 mol/l perchloric acid. The homogenate was allowed to stand for approximately 10 min, centrifuged, and the radioactivity determined in 1.0 ml aliquots of the supernatant. The amounts of radioactivity present in 1.0 ml aliquots of the incubation medium, after completion of incubation, were also determined by liquid scintillation counting, and the tissue-medium concentration ratio was then calculated as (d $min^{-1} g^{-1}$ of tissue)/(d $min^{-1} ml^{-1}$ of incubation medium). Corrections were made for counting efficiency by the use of an external reference standard.

Statistical analysis of data

Unpaired, 2-tailed Student's *t* tests were used to test for statistically significant differences between means. Probability (*P*) levels corresponding to the calculated values of *t* are given in the text; $P < 0.05$ was taken to indicate a significant difference.

Drugs and radiochemicals

The following drugs were used: atropine sulphate (British Drug Houses); cimetidine (Smith, Kline & French Laboratories); cocaine hydrochloride (Drug Houses of Australia); impromidine trihydrochloride (Smith, Kline & French Laboratories); mepyramine maleate (May & Baker); phentolamine mesylate (Ciba); 2-(2-pyridyl)-ethylamine dihydrochloride (PEA; Smith, Kline & French Laboratories).

Tritiated noradrenaline (1-[7-,8-^{3}H]-noradrenaline) was obtained from the New England Nuclear Corporation or the Radiochemical Centre (Amersham); the specific activity of the samples ranged from 10.0 to 10.4 Ci/mmol.

Results

Effects of impromidine on the rate and force of atrial beating and on the resting efflux of radioactivity

Impromidine caused marked increases in the rate and force of beating of the atria. The threshold concentration was approx. 3 nmol/l and the maximal effect was obtained with approx. 1 μmol/l impromidine. These findings are in agreement with those of Durant *et al.* (1978).

Impromidine in concentrations of 3 to 100 nmol/l had no effect on the resting release of radioactivity from atria labelled with [^{3}H]-noradrenaline.

Effect of impromidine on the stimulation-induced efflux of radioactivity and on responses to sympathetic stimulation

In control preparations, the stimulation-induced (S-I) efflux of radioactivity released in the first period of stimulation (2 Hz, for 10 s) was 10784 d/min (s.e.mean = 1350, $n = 19$). The S-I efflux with the second period was 71.0% (s.e.mean = 2.3, $n = 19$) of that for the first period.

Impromidine had no significant effect on the S-I efflux in concentrations of 3, 10 and 25 nmol/l, but in higher concentrations of 50 and 100 nmol/l, impromidine increased S-I efflux to about 140% of the control value (Figure 1).

Although the present experiments were not designed to quantitate effects on the inotropic and chronotropic responses to stimulation, it was clear that, in contrast to its effects on S-I efflux, impromidine (3–100 nmol/l) reduced these responses. The extent of the reduction in the chronotropic responses appeared to be dependent on the direct positive chronotropic effect of impromidine. Thus the greater the effect of impromidine on the basal rate of atrial contractions, the greater the inhibition of the response to stimulation. A similar dependence was previously observed in guinea-pig atria between the chronotropic effect of histamine and inhibition of the chronotropic response to sympathetic stimulation by histamine (Rand *et al.*, 1981).

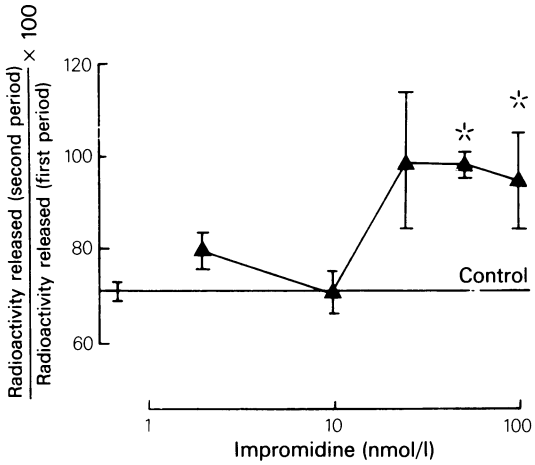

Figure 1 The effect of impromidine (3–100 nmol/l) on stimulation-induced efflux of radioactivity from guinea-pig atria which had been previously incubated in [^{3}H]-noradrenaline. The atrial intramural sympathetic nerves were stimulated in two 10 s periods with a 22 min interval at a frequency of 2 Hz. The horizontal axis represents the impromidine concentration (nmol/l). The vertical axis shows the stimulation-induced effluxes of radioactivity in second periods of stimulation expressed as percentages of that in first periods; the mean control value is represented by the horizontal line. Each point represents the mean of 4 to 8 experiments. Vertical bars represent s.e.means. $^*P < 0.01$.

Effect of impromidine in the presence of H_1- and H_2-receptor antagonists

The increases in rate and force of atrial beating in the presence of impromidine were diminished by 10 μmol/l of cimetidine and abolished by 30 μmol/l. The enhancement of S-I efflux produced by 50 nmol/l of impromidine was abolished by cimetidine in a concentration of 30 μmol/l, but 10 μmol/l of cimetidine had no significant effect (Figure 2). Mepyramine (0.1 μmol/l) had no effect on the increases in rate and force of atrial contractions produced by impromidine. However, mepyramine (0.1 μmol/l) abolished the enhancing effect of impromidine on S-I efflux (Figure 2).

Block of uptake of [^{3}H]-noradrenaline

In view of the possibility that impromidine may have increased S-I efflux of radioactivity by blocking up-

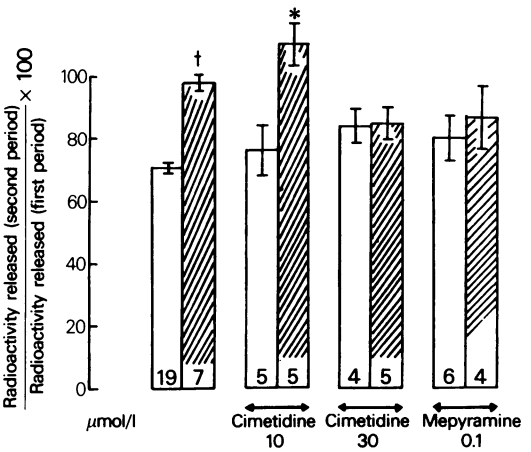

Figure 2 The effect of impromidine (50 nmol/l) in the absence and presence of cimetidine (10 and 30 μmol/l) or mepyramine (0.1 μmol/l) on stimulation-induced efflux of radioactivity from guinea-pig atria previously incubated in [^{3}H]-noradrenaline. The columns represent the efflux of radioactivity in the second period of stimulation as a percentage of the efflux in the first period. The blocking drugs were present throughout the experiment. Impromidine was present only during the second period of stimulation. Hatched columns show the effect of impromidine; open columns are corresponding control experiments. Vertical bars indicate s.e.means. The number of experiments of each type is indicated at the foot of each column. *$P = 0.005$; †$P < 0.001$.

take mechanisms for noradrenaline, the effect of impromidine on uptake of [^{3}H]-noradrenaline by guinea-pig atria was investigated. Impromidine in a concentration of 10 nmol/l had no effect, but concentrations of 50 nmol/l and 100 nmol/l significantly ($P < 0.05$) decreased the amount of [^{3}H]-noradrenaline taken up by the atria (Figure 3).

The effect of impromidine on S-I efflux was investigated after blockade of neuronal uptake with cocaine (30 μmol/l). Impromidine (50 nmol/l) increased S-I efflux in the presence of cocaine to the same extent as in its absence (Table 1).

Effect of impromidine in the presence of phentolamine

Blockade of prejunctional α-adrenoceptors at noradrenergic neuroeffector sites is known to increase transmitter release (Starke, 1977). To exclude the possibility that impromidine may increase transmitter release by an action on prejunctional α-adrenoceptors, its effect was determined in the presence of phentolamine in a sufficient concentration to block these receptors.

Phentolamine (30 μmol/l) had no effect on resting efflux but significantly increased the amount of radioactivity released with the first period of stimulation compared to control experiments by a factor of more than 2.5 fold; nevertheless, impromidine (50 nmol/l) still significantly increased S-I efflux in the presence of phentolamine (Table 1).

Effect of 2-(2-pyridyl)-ethylamine

In view of the effects of impromidine on S-I efflux, it was of interest to investigate the effect of 2-(2-pyridyl)-ethylamine (PEA), a relatively specific H_1-receptor agonist, on S-I efflux.

The effects of PEA in concentrations of 10, 30 and 100 μmol/l and of PEA (30 μmol/l) in the presence of mepyramine (0.1 μmol/l) and in the presence of the β-adrenoceptor antagonist metoprolol (0.1 μmol/l) on the resting and S-I efflux of radioactivity are summarized in Table 2. PEA significantly increased both the resting and the S-I efflux of radioactivity ($P < 0.01$), the increase in both parameters being greater with the higher concentrations. The effects of PEA (30 μmol/l) were unaltered by the presence of mepyramine (0.1 μmol/l) or metoprolol (0.1 μmol/l) (Table 2).

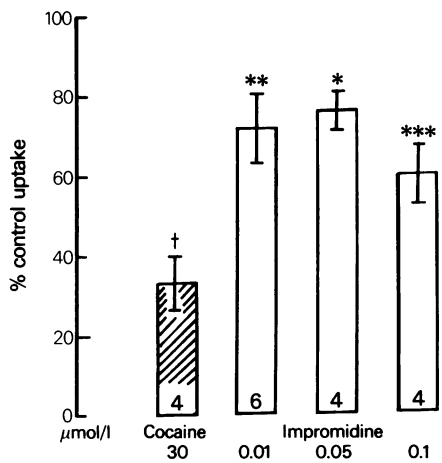

Figure 3 The effect of impromidine on the uptake of radioactivity by guinea-pig atria during a 10 min period of incubation in [^{3}H]-noradrenaline (0.4 μmol/l, 4 μCi/ml). The columns represent the mean tissue/medium ratios of radioactivity ($d\,min^{-1}\,g^{-1}$ tissue)/($d\,min^{-1}\,ml^{-1}$ incubation medium) in the presence of cocaine or impromidine expressed as a percentage of that in control experiments with no drug present. The vertical bars represent s.e.means and the number of experiments performed is indicated within each column. The control tissue/medium ratio of radioactivity was 5.11 (s.e.mean = 0.32, $n = 9$). *$P = 0.018$; **$P = 0.008$; ***$P = 0.002$; †$P < 0.001$.

Table 1 Effects of cocaine (30 μmol/l) and phentolamine (5 μmol/l) on the facilitation of S-I efflux of radioactivity produced by impromidine (50 nmol/l)

Drug present in S_1 *and* S_2	*S-I efflux*			
	Control		*Impromidine*	
	S_1 (d/min)	$S_2/S_1 \times 100\%$	S_1 (d/min)	$S_2/S_1 \times 100\%$
	10784 ± 1350 $n = 19$	71.0 ± 2.3	7550 ± 1554 $n = 7$	98.0 ± 2.6 $P < 0.001$
Cocaine (30 μmol/l)	†15211 ± 1901 $n = 6$	71.4 ± 6.4	†11630 ± 718 $n = 4$	96.3 ± 2.7 $P < 0.001$
Phentolamine (5 μmol/l)	†26776 ± 2191 $n = 8$	89.4 ± 4.8	†21713 ± 2421 $n = 4$	107.5 ± 9.5 $P < 0.05$

Cocaine or phentolamine was added 30 min before the first period of stimulation (S_1) and then remained present throughout the experiment. Impromidine was added 15 min before the second period of stimulation (S_2). The results are expressed as mean ± s.e. n is the number of experiments. The probability values (P) for the significance of the effects of impromidine on the mean values of S_2/S_1 are given and † denotes significant effects ($P < 0.01$) of phentolamine and cocaine on S-I effluxes in S_1 compared to experiments in their absence.

Table 2 Effects on resting and stimulation-induced effluxes of 2-(2-pyridyl)-ethylamine (PEA, 10, 30 and 100 μmol/l), PEA (30 μmol/l) in the presence of mepyramine (0.1 μmol/l), and PEA (30 μmol/l) in the presence of metoprolol (0.1 μmol/l)

Drug present in S_1 *and* S_2	*PEA present in* S_2	*Resting efflux* ($R_2/R_1 \times 100\%$)	*S-I efflux* ($S_2/S_1 \times 100\%$)
—	—	80.2 ± 1.9 $n = 19$	71.0 ± 2.3
—	10 μmol/l	*167.8 ± 11.3 $n = 4$	*117.0 ± 8.2
—	30 μmol/l	*248.0 ± 4.7 $n = 7$	*138.0 ± 23
—	100 μmol/l	*294.0 ± 41 $n = 5$	*144.1 ± 25
Mepyramine 0.1 μmol/l	—	84.2 ± 1.9 $n = 6$	80.2 ± 7.5
Mepyramine 0.1 μmol/l	30 μmol/l	*217.0 ± 9 $n = 4$	150.4 ± 20
Metoprolol 0.1 μmol/l	—	90.3 ± 3.5 $n = 3$	*44.0 ± 1.5
Metoprolol 0.1 μmol/l	30 μmol/l	*200.6 ± 17.9 $n = 5$	*127.0 ± 18.3

S_1 no drug = 10784 ± 1350 d/min; S_1 mepyramine = 10550 ± 1142 d/min; S_1 metoprolol = 16242 ± 2209 d/min. PEA was added 15 min before the second period of stimulation (S_2). Mepyramine and metoprolol were added 30 min before the first period of stimulation (S_1) and remained present throughout the experiment. The resting and stimulation-induced effluxes for the second periods of stimulation are expressed as percentages of those for first (control) periods. The data are given as mean ± s.e. and the number of observations (n) are indicated. The asterisks indicate significant differences in the mean values of R_2/R_1, and S_2/S_1 in the presence of PEA compared to corresponding control values.

Discussion

The ability of histamine to inhibit responses to noradrenergic nerve stimulation by activating prejunctional receptors has previously been reported for canine saphenous vein and tibial artery strips (McGrath & Shepherd, 1976), the canine heart *in situ* (Lokhandwala, 1978), the canine isolated blood-perfused gracilis muscle (Powell, 1979) and guinea-pig isolated atria (Wong-Dusting *et al.*, 1979; Rand *et al.*, 1982). The histamine receptors involved appeared to be of the H_2-type.

In the present study, impromidine, a highly specific agonist on postjunctional histamine H_2-receptors (Durant *et al.*, 1978), did not mimic the prejunctional inhibitory actions of histamine on guinea-pig isolated atria. In view of the relative potencies of impromidine and histamine at H_2-receptors (Durant *et al.*, 1978), the concentrations of impromidine which increased transmitter noradrenaline release (25, 50 and 100 nmol/l) are comparable to the concentrations of histamine previously found to inhibit transmitter release in guinea-pig atria (Rand *et al.*, 1982). However, this facilitatory effect of impromidine was not concentration-dependent and all three concentrations increased S-I efflux to the same extent (i.e., approximately 40%). Furthermore, the actions of impromidine were blocked by both the histamine H_1-receptor antagonist, mepyramine (0.1 μmol/l) and the H_2-receptor antagonist, cimetidine (30 μmol/l). This suggests that the effect of impromidine on S-I efflux may be nonspecific.

Impromidine increased the rate and force of atrial contractions, and cimetidine abolished these effects, indicating an H_2-receptor site of action postjunctionally. We have previously shown that resting and S-I release of radioactivity is unrelated to the mechanical activity of the atria (Rand *et al.*, 1982); thus it is unlikely that the facilitation of S-I efflux by impromidine is due to its positive chronotropic and inotropic effects.

It was considered possible that impromidine may have enhanced S-I efflux in guinea-pig atria by blocking the uptake mechanisms for transmitter noradrenaline. Therefore, the effect of impromidine on the uptake of [^{3}H]-noradrenaline by guinea-pig atria was investigated. Impromidine was found to have some uptake blocking activity at 50 nmol/l and 100 nmol/l concentrations. However, blockade of neuronal uptake could not account entirely for the enhancement of transmitter release by impromidine, since the enhancement was still present in the presence of the neuronal uptake blocker cocaine (30 μmol/l); an increase in concentration of neuronal uptake blocking drugs above that which is maximal for enhancing S-I efflux (approximately 1 μmol/l for cocaine) actually decreases transmitter release (Rand, McCulloch & Story, 1975). It is also unlikely that impromidine is increasing transmitter release by entering noradrenergic nerves and releasing [^{3}H]-noradrenaline directly from the transmitter stores, as the resting efflux of radioactivity was unaffected by impromidine.

Blockade of prejunctional α-adrenoceptors is known to increase the release of transmitter noradrenaline (Starke, 1977). However, impromidine does not appear to be enhancing transmitter release through blockade of prejunctional α-adrenoceptors, as S-I efflux was still enhanced in the presence of phentolamine in sufficient concentration to block these receptors.

Impromidine appears to act as a partial agonist on histamine receptors in the rat isolated uterus and stomach (Durant *et al.*, 1978; Parsons & Sykes, 1980), the rabbit stomach (Curwain & Turner, 1981), and in the guinea-pig isolated gastric cells (Lewin, Grelac, Cheret, Rene & Bonfils, 1979) and papillary muscle (Bertaccini & Coruzzi, 1981). Histamine has been reported to be released during sympathetic nerve stimulation in the guinea-pig isolated perfused heart (Levi & Roby, 1981) and in the dog heart *in situ* (Karch, Ingram, Oravec & Cohen, 1977). Thus it is possible that as a partial agonist at inhibitory prejunctional histamine H_2-receptors, impromidine may compete with histamine to produce a relative increase in transmitter noradrenaline release, that is, impromidine may increase transmitter release by antagonizing the inhibition of release mediated by endogenous histamine. Such an interaction has been shown between clonidine (partial agonist) and transmitter noradrenaline at prejunctional α-adrenoceptors associated with the noradrenergic nerves in guinea-pig atria (Medgett, McCulloch & Rand, 1978). However, in guinea-pig isolated atria, impromidine appears to act as a full agonist on postjunctional H_2-receptors, eliciting a maximum chonotropic response which is 98.7% that of histamine (Durant *et al.*, 1978). Furthermore, the facilitatory effect of impromidine on S-I efflux is not concentration-dependent. Thus it seems unlikely that impromidine is acting as a partial agonist prejunctionally.

The relatively specific H_1-receptor agonist 2-(2-pyridyl)-ethylamine (Durant *et al.*, 1975) was found to increase both resting and stimulation-induced effluxes of transmitter noradrenaline. This effect was not due to activation of H_1-receptors as it was unaltered in the presence of mepyramine. Release of noradrenaline from guinea-pig atria by this compound has previously been observed by Hughes (1980). Also, Flynn, Gristwood & Owen (1979) have reported that, in the guinea-pig isolated heart, the positive chronotropic effects of 2-(2-pyridyl)-ethylamine were not antagonized by cimetidine or mepyramine but were antagonized by the β_1-

adrenoceptor antagonist propranolol. Although prejunctional facilitatory β-adrenoceptors are known to be present in this tissue (Majewski, McCulloch, Rand & Story, 1980), 2-(2-pyridyl)-ethylamine did not appear to be facilitating transmitter noradrenaline release by activating these receptors, as the presence of metoprolol did not alter its effects.

Thus, it appears that the relatively specific H_1-receptor agonist, 2-(2-pyridyl)-ethylamine, and the specific H_2-receptor agonist, impromidine, have actions on noradrenergic nerves in guinea-pig atria other than stimulation of histamine H_1-and H_2-receptors which make them unsuitable for use in the classification of the type of histamine receptor that is involved in the prejunctional action of histamine.

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