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Pentazocine-induced Catecholamine Efflux from the Dog Perfused Adrenals

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Abstract—This study has been undertaken to determine whether pentazocine induces catecholamine efflux from the adrenal medulla as a mechanism for its sympathomimetic effect. Dog isolated adrenals were perfused retrogradely with modified Locke's solution. The efflux of catecholamines from dog perfused adrenals was increased from the resting output of $0{\cdot}18 \pm 0{\cdot}04$ μg min^{-1} (mean ± s.e.), to $0{\cdot}47 \pm 0{\cdot}13$ μg min^{-1} by the administration of pentazocine (50 μM). The pentazocine-induced catecholamine efflux was dose-dependent in the 50–400 μM dose range. This effect of pentazocine was not inhibited by either a combination of atropine and (+)-tubocurarine, or verapamil, in contrast to acetylcholine-induced catecholamine release. There was no significant difference in potency among stereoisomers, i.e. (+)-, (−)- and (±)-pentazocine, in inducing catecholamine efflux. Naloxone did not influence the effects of either (+)- or (−)-pentazocine. The interaction of pentazocine with acetylcholine-induced catecholamine release was also examined. Both (+)- and (−)-pentazocine inhibited acetylcholine-induced catecholamine release dose-dependently, and these inhibitory effects were not reversed by naloxone. Acetylcholine-induced catecholamine release was accompanied by increased dopamine-β-hydroxylase release, whereas pentazocine-induced catecholamine efflux was not. These results suggest that pentazocine directly acts on the adrenal medulla to induce catecholamine efflux via a non-exocytotic mechanism, and that opioid receptors do not play a role in this action.

Pentazocine has been shown to increase the circulation of both noradrenaline and adrenaline, accompanied by a rise in blood pressure and heart rate in man (Tammisto et al 1971; Manner et al 1987) to increase systemic and pulmonary artery pressures and systemic vascular resistance in cardiac patients (Lee et al 1976), and to reverse haemodynamic changes associated with anaphylactic shock in rats (Paciorek et al 1985). These effects appear to be mediated by facilitation of sympathetic neurotransmission (Takki et al 1973), but whether these are effects exerted through a central mechanism or are direct actions on the peripheral sympatho-adrenal system has not been ascertained.

We have investigated whether pentazocine acts directly on the adrenal medulla to induce catecholamine efflux, and studied the mechanism of this action.

Materials and Methods

Retrograde perfusion of the adrenal glands

Mongrel dogs of either sex, 7–13 kg, were anaesthetized with sodium pentobarbitone (30 mg kg^{-1} i.v.). Both adrenals were exposed through a midline abdominal incision and isolated outside the body together with the adrenolumbar vein. The details of the procedure for perfusing dog adrenals have been described previously (Sumikawa et al 1982). The adrenolumbar vein was cannulated, and the glands were retrogradely perfused, at a pressure ranging from 45 to 80 cm H_2O, with a warmed (37°C) modified Locke's solution that was aerated with 95% CO_2–5% O_2. The composition of the standard solution was as follows (mM): NaCl 154, KCl 5·6, $CaCl_2$ 2·2, glucose 10 and Tris-HCl buffer (pH 7·4) 40. Perfusion was carried out at a constant rate ranging from 0·9 to 1·3 mL min^{-1} in each experiment. About 80 min was allowed to elapse before any treatment for reduction of spontaneous efflux of catecholamines. Drugs dissolved in Locke's solution were administered by continuous infusion by switching a valve on the tubes leading to the glands. The effluent from the adrenals was collected evey 2 min into glass tubes kept on ice, starting 2 min before drug administration, and lasting until the end of drug administration.

Experiment to determine the stimulatory effect of pentazocine

The stimulatory action of pentazocine was examined by adding 25 to 400 μM to the standard solution. The adrenals were stimulated two or three times for a period of 10 min each, followed by 30 min recovery intervals. To examine the opiate receptor-related specificity, the effects of (−)- and (+)-pentazocine, and morphine, were studied.

In experiments to examine the effect of naloxone, verapamil or a combination of atropine and (+)-tubocurarine on the pentazocine action, the adrenals were perfused with a solution containing each of these compounds during a period starting 8 min before the second stimulation and lasting until the end of the second stimulation. The effects of verapamil, or of a combination of atropine and (+)-tubocurarine on the acetylcholine-induced catecholamine release were also examined in the same manner as pentazocine.

Interaction between pentazocine and acetylcholine

The adrenals were stimulated with 10 μM acetylcholine for three periods each of 6 min, with 30 min recovery intervals in between. Pentazocine was added to the solution starting 8 min before the second stimulation and lasting until the end of the second stimulation. The third stimulation was done in the

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absence of pentazocine to examine the reversibility of the effect of pentazocine. The effect of naloxone on the interaction of pentazocine with acetylcholine was examined by using 0·1, 1 or 10 μM naloxone in combination with pentazocine.

Measurement of catecholamines and dopamine-β-hydroxylase and lactate dehydrogenase

Catecholamines were measured by automated HPLC using a chemical detector (Irika Co., Kyoto, Japan), in which adrenaline and noradrenaline were determined differentially (Kissinger 1975). These compounds were separated by reverse-phase chromatography using a packed column RP-18 (Irika Co., Kyoto, Japan) and a mobile phase consisting of 0·1 M sodium dihydrogen phosphate buffer containing EDTA (0·05 mM), octanesulphonic acid (1 mM) and 5% acetonitrile. The glassy carbon working electrode was set at +700 mV. This assay system has a limit of sensitivity of 10 pg mL^{-1} for adrenaline and noradrenaline, and the inter- and intra-assay variations are less than 3%.

Lactate dehydrogenase (LDH) was measured by Wacker's method, using an auto-analyser (Amador et al 1963). Dopamine-β-hydroxylase (DBH) activity was measured by the method of Nagatsu & Udenfriend (1972), in which tyramine was used as substrate and the octopamine formed was measured by spectrophotometry. An 0·8 mL sample of each fraction was used for the assay, and DBH activity was expressed as nanomoles of product (octopamine) formed per hour per mL of effluent (nmol h^{-1} mL^{-1}). It was ascertained that the drugs used did not interfere with the assay of catecholamine or DBH activity.

Stimulant-induced catecholamine efflux was calculated as the difference between spontaneous catecholamine efflux and efflux during stimulation. The degree of inhibition on catecholamine efflux was expressed by the second stimulation value as per cent of the first stimulation value in order to minimize the individual variations.

Drugs

The optical enantiomers of pentazocine were separated from the racemate (Yamanouchi Pharmacological Company, Tokyo, Japan) by using (−)- or (+)-binaphthyl phosphoric acid, and structural purity was ascertained by nuclear magnetic resonance. The optically-assessed purities of (−)- and (+)-pentazocine were 96·25 and 95·30%, respectively. Pentazocine isomers were dissolved in several drops of lactic acid as a 20 mM stock solution. All drug solutions were prepared by dissolving the agents into the perfusion fluid and all solutions for perfusion were adjusted to pH 7·4.

Statistical analysis

These data were expressed as mean ± s.e. The results of repeated measurements and multiple groups were analysed by one-way analysis of variance. Pairwise comparisons between groups were assessed by Student's *t*-test. $P<0.05$ was considered significant.

Results

Effect of pentazocine on the efflux of catecholamines from the adrenals

The rate of spontaneous efflux of catecholamines (noradrenaline plus adrenaline) during the 2 min before drug administration was 0·18 ± 0·04 μg min^{-1} (0·17 ± 0·04 μg mL^{-1}, mean ± s.e.m., n = 15). During administration of pentazocine (100 μM) both noradrenaline and adrenaline efflux increased gradually and attained a maximum rate within 6–10 min. The peak rate of catecholamine efflux was 0·53 ± 0·15 μg min^{-1} (0·51 ± 0·14 μg mL^{-1}, n = 4). A high reproducibility of increase in output of catecholamines in the effluent was observed after the second and third exposures to the same concentration of pentazocine at 30 min intervals (Fig. 1).

Table 1 shows the ratio of noradrenaline and adrenaline in the effluent. Stimulation by acetylcholine showed a tendency to increase the proportion of noradrenaline in the effluent, whereas pentazocine did not alter the relative proportions of adrenaline and noradrenaline.

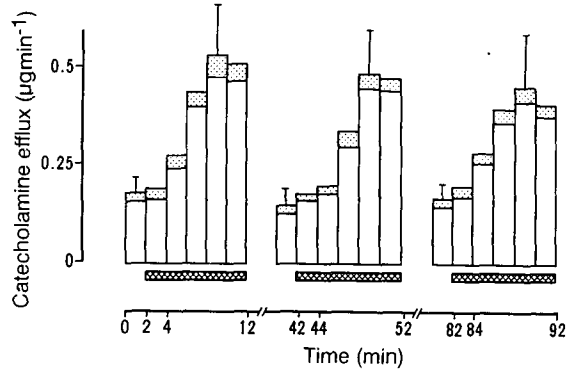

FIG. 1. Pentazocine-induced catecholamine efflux from dog isolated perfused adrenals. The ordinate represents the rate of catecholamine release during a 2 min period (n = 4, mean ± s.e.m. for each value). The adrenals were perfused with a modified Locke's solution at 37°C and exposed three times to 100 μM pentazocine. The exposure period was 10 min, followed by 30 min recovery intervals. Pentazocine (100 μM), cross hatched columns; noradrenaline, dotted columns; adrenaline, open columns.

Table 1. Noradrenaline/adrenaline + noradrenaline ratio of catecholamines during the perfusion with pentazocine and acetylcholine.

	Resting output			Peak output during the drug perfusion		
Drugs	Noradrenaline (μg min^{-1})	Adrenaline (μg min^{-1})	Noradrenaline /adrenaline + noradrenaline (%)	Noradrenaline (μg min^{-1})	Adrenaline (μg min^{-1})	Noradrenaline /adrenaline + noradrenaline (%)
Pentazocine (100 μM)	0·023 ± 0·007	0·14 ± 0·05	14·5 ± 3·0	0·07 ± 0·01*	0·46 ± 0·14*	13·4 ± 1·3
Acetylcholine (10 μM)	0·021 ± 0·006	0·16 ± 0·06	13·5 ± 1·2	0·42 ± 0·07*	1·86 ± 0·22**	18·3 ± 1·9*

*$P<0.05$ and **$P<0.001$ compared with resting output value.

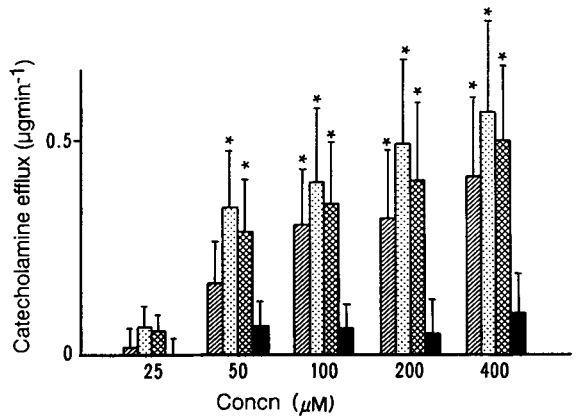

FIG. 2. Concentration-effect relationships with respect to the effect of morphine and optical enantiomers of pentazocine on inducing catecholamine efflux from dog perfused adrenals. The ordinate represents the maximum rate of catecholamine efflux induced by (−)-, (+)- and (±)-pentazocine (left-hatched, dotted and cross-hatched columns, respectively), and morphine (closely dotted columns) (mean ± s.e.m., n = 4–6 for each value). * Significant difference from control at $P < 0.05$.

Fig. 2 shows the dose-effect relationship of pentazocine and morphine on catecholamine efflux. Racemic pentazocine, as well as (+)- and (−)-pentazocine, showed this effect at concentrations of 50 μM or more. Although (+)-pentazocine tended to induce catecholamine efflux more potently than racemate or (−)-pentazocine, there was no significant difference among them. By contrast, morphine exerted no effect on catecholamine efflux even at concentrations up to 400 μM. Naloxone failed to influence the effects of either (+)- or (−)-pentazocine on catecholamine efflux (Fig. 3).

Fig. 4 shows the effects of cholinergic antagonists on the

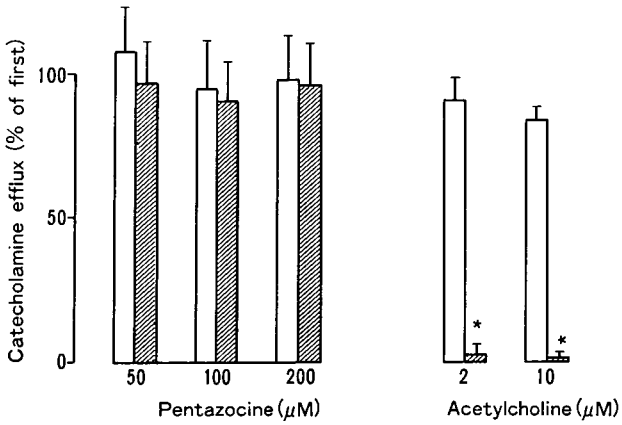

FIG. 4. Effects of an acetylcholine antagonist on acetylcholine- or pentazocine-induced catecholamine efflux from dog perfused adrenals. The adrenals were stimulated twice with acetylcholine (2, 10 μM) or pentazocine (50, 100, 200 μM) for 10 min at 30 min intervals. Atropine (50 μM) and (+)-tubocurarine ((+)Tc, 10 μM) were added to the solution during the period from 8 min before the second stimulation and lasting until its end. The ordinate represents the second stimulation value compared with the first stimulation value (mean + s.e.m., n = 4 for each value). * Significant difference from control at $P < 0.05$. Control, open columns; 50 μM atropine + 10 μM (+)Tc, left-hatched column.

catecholamine efflux induced by pentazocine, in comparison with that on the catecholamine release induced by acetylcholine. Acetylcholine-induced catecholamine release was completely inhibited by a combination of 50 μM atropine and 10 μM (+)-tubocurarine. However, pentazocine-induced catecholamine efflux was not influenced by these cholinergic antagonists.

Verapamil markedly reduced acetylcholine-induced catecholamine release, but showed no inhibitory effect on pentazocine-induced catecholamine efflux (Fig. 5).

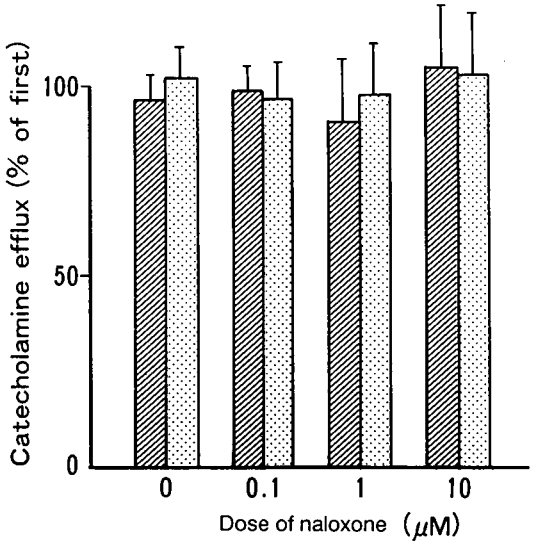

FIG. 3. Effects of naloxone on pentazocine-induced catecholamine efflux from dog perfused adrenals. The adrenals were stimulated with (−)-, or (+)-pentazocine (left-hatched and dotted columns, respectively) (100 μM). Naloxone (0·1–10 μM) was added to the solution during the period from 8 min before the second stimulation and lasting until its end. The ordinate represents the second stimulation value compared with the first stimulation value (mean ± s.e.m., n = 4–6 for each value).

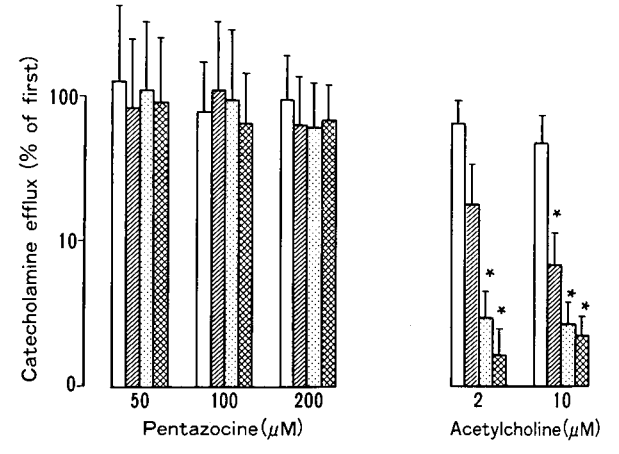

FIG. 5. Effects of calcium channel inhibitor on acetylcholine- or pentazocine-induced catecholamine efflux from perfused dog adrenals. The adrenals were stimulated twice with acetylcholine (2, 10 μM) or pentazocine (50, 100, 200 μM) for 10 min at 30 min intervals. Verapamil (4, 20, 100 μM, left-hatched, dotted and cross-hatched columns, respectively) was added to the solution during the period from 8 min before the second stimulation and lasting until its end. The ordinate represents the second stimulation value compared with the first stimulation value (mean ± s.e.m, n = 4–6 for each value). * Significant difference from control (open columns) at $P < 0.05$.

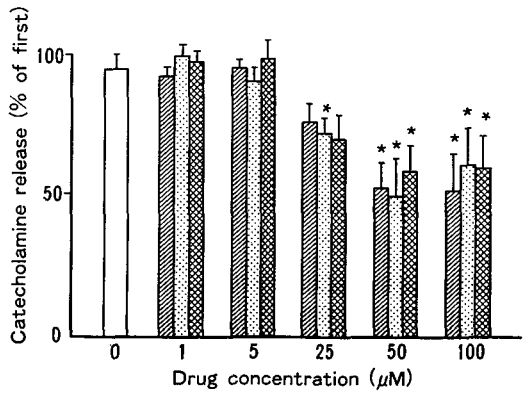

FIG. 6. The inhibitory effects of enantiomers of pentazocine on acetylcholine-induced catecholamine release from the adrenal medulla. The adrenals were stimulated three times with 10 μM acetylcholine for 6 min at 30 min intervals. The second stimulation was performed in the presence or absence of (−)-, (+)- and (±)-pentazocine (left-hatched, dotted and cross-hatched columns, respectively). The ordinate represents the second stimulation value compared with the first stimulation value (mean ± s.e.m., n = 4 for each value). *Significant difference from control (open columns) at $P < 0.05$.

Efect of pentazocine on acetylcholine-induced catecholamine release

In controls, during the stimulation periods of 10 μM acetylcholine for 6 min at 30 min intervals, a high reproducibility of catecholamine release was observed. The peak rate of catecholamine release at the second and the third responses were 94·5 ± 5·1 and 84·1 ± 6·8% of the first response, respectively (four glands). Racemic pentazocine, as well as (+)- and (−)-pentazocine, significantly inhibited the catecholamine release induced by the second stimulation of acetylcholine as compared with control (Fig. 6). This effect of pentazocine was reversible, because the third response after washing out pentazocine for 30 min was restored to the control level (approximately 85% of the first response). Naloxone failed to influence the inhibitory effect of either (+)- or (−)-pentazocine on acetylcholine-induced catecholamine release (Fig. 7).

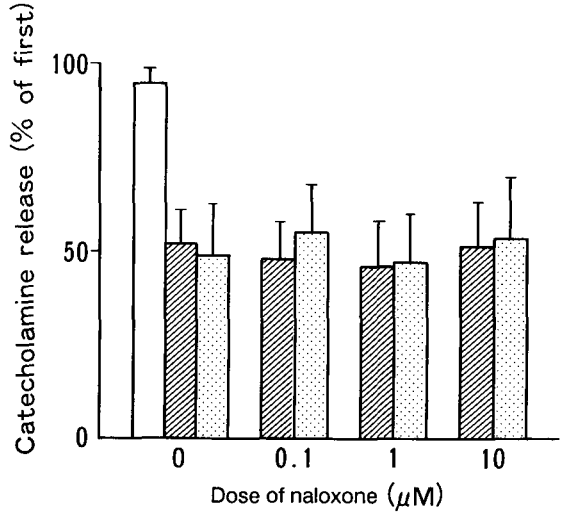

FIG. 7. Effects of naloxone on the inhibitory effect of pentazocine on acetylcholine-induced catecholamine release. The adrenals were stimulated with acetylcholine (10 μM). Naloxone (0·1–10 μM) was added to the solution in combination with pentazocine (50 μM) during the period from 8 min before the second stimulation and lasting until its end. The ordinate represents the second stimulation value compared with the first stimulation value (mean ± s.e.m., n = 4 for each value). Control, open columns; (−)-pentazocine, left-hatched columns; (+)-pentazocine, dotted columns.

Table 2. Effects of pentazocine and acetylcholine on the release of catecholamine, dopamine β-hydroxylase and lactate dehydrogenase from dog adrenals.

	Spontaneous release	Acetylcholine (1 μM)	Pentazocine (100 μM)
CA	0·15 ± 0·03	0·63 ± 0·09*	0·51 ± 0·14*
DBH	2·1 ± 0·5	6·8 ± 1·4*	2·7 ± 0·6†
LDH	5·3 ± 0·6	4·9 ± 0·9	5·7 ± 0·5

CA, catecholamine (μg mL^{-1}); DBH, dopamine β-hydroxylase activity (nmol octopamine formed h^{-1} mL^{-1}), LDH, lactate dehydrogenase (units L^{-1}), *$P < 0.05$ compared with spontaneous release value. †$P < 0.05$ compared with acetylcholine value.

DBH and LDH activity in the perfusate

The effects of acetylcholine and pentazocine on the release of DBH and LDH in relation to catecholamine release are shown in Table 2. Acetylcholine-induced catecholamine release was accompanied by increased DBH release, whereas pentazocine-induced catecholamine efflux was not. There was no increased efflux of LDH during stimulation of the adrenals by either acetylcholine or pentazocine.

Discussion

Alderman et al (1972) reported that pentazocine elevated aortic pressure (+12·5%), left ventricular end-diastolic pressure (+20·2%) and pulmonary-artery pressure (+36·3%) in patients with coronary heart disease. Lee et al (1976) also reported similar effects in patients with acute myocardial infarction. Tammisto et al (1971) reported that plasma noradrenaline and adrenaline concentrations after administration of pentazocine increased (170–200 and 180–200% of pre-administration values, respectively) in man. Manner et al (1987) also showed significant elevation of plasma adrenaline and noradrenaline in man. The elevation of the plasma adrenaline level in these reports indicates that there is a contribution of sympatho-adrenal stimulation by pentazocine, because adrenals are substantially the only source of plasma adrenaline both in man and dog (Anton & Sayre 1962). To examine the site of pentazocine-action, Takki et al (1973) studied the effect of epidural blockade on pentazocine-induced increase in plasma catecholamines and blood pressure in man, and showed that epidural blockade prevented the pressor response to pentazocine but failed to cause any significant difference in plasma catecholamine levels. Although they believed the site of pentazocine-induced sympathetic stimulation was central, it has not been verified.

Sellevold et al (1985) reported a case of pheochromocytoma in which pentazocine caused a marked increase in blood pressure in spite of the presence of spinal blockade. In this case, the pressor response to pentazocine seemed to be mediated not by a central action but by a direct action on

tumour cells to induce catecholamine efflux, because the spinal anaesthesia would block sympathetic discharge, and furthermore, tumour cells ordinarily have no sympathetic innervation (Winkler & Smith 1968).

The present results show that pentazocine acts directly on the adrenal medullary cells to induce catecholamine efflux. This action is dose-dependent and completely reversible. Pentazocine increases both noradrenaline and adrenaline in the effluent from the adrenals and the proportion of noradrenaline and adrenaline is not changed from the resting output. By contrast, the increase in the ratio of noradrenaline was reported when the dog adrenals were stimulated with acetylcholine (Tsujimoto & Nishikawa 1975). In the present study, the ratio of noradrenaline in the effluent was also increased by the stimulation with 10 μM acetylcholine. Although it is not known whether this difference in the proportion of the catecholamines has any physiological significance, it is suggested that a different mechanism might be involved in the action of these compounds.

Acetylcholine is the physiological transmitter which causes the adrenal medulla to release catecholamines, and pentazocine may cause acetylcholine release from the sympathetic nerve endings in the adrenals, resulting in secondary release of catecholamines. However, this mechanism is unlikely, because a combination of atropine and (+)-tubocurarine inhibited acetylcholine-induced catecholamine release completely, whereas it failed to affect pentazocine-induced catecholamine efflux. Furthermore, pentazocine inhibited acetylcholine-induced catecholamine release dose-dependently, indicating that pentazocine has an inhibitory effect on the physiological stimulus-secretion coupling. Thus, centrally-mediated-sympathetic discharge would be blocked at this site by pentazocine in a similar way to some intravenous anaesthetics (Sumikawa et al 1983).

Opioid receptors have been shown to exist in the chromaffin cells and to play a significant role in moderating catecholamine release (Saiani & Guidotti 1982). Most opioid receptors in adrenal medullary cells are κ-receptors (Castanas et al 1983, 1985a, b). Pentazocine is a benzomorphan derivative and is considered to have κ- and σ-agonistic activities and weak μ-receptor antagonistic action (Martin 1983). The present findings indicate that the actions of pentazocine, i.e. both the stimulatory effect on catecholamine efflux and the inhibitory effect on acetylcholine-induced catecholamine release, would not be mediated by opioid receptors, because naloxone failed to inhibit the pentazocine actions, and there was no stereospecificity in the effects of pentazocine.

It has been well established that Ca^{2+} is the coupler in the stimulus-secretion coupling of the adrenal medullary cells and that the entry of Ca^{2+} into the cell triggers exocytotic secretion of catecholamines. To determine whether exocytosis was involved in the pentazocine-induced catecholamine efflux, we examined the effect of verapamil on pentazocine-induced catecholamine efflux, and the effect of pentazocine on the release of DBH-biochemical evidence for exocytotic release of catecholamines. Verapamil significantly inhibited acetylcholine-induced catecholamine release, but exerted no influence on pentazocine action. Concomitant secretion of catecholamines and DBH was observed in response to stimulation by acetylcholine, whereas pentazocine-induced catecholamine efflux was not accompanied by DBH release. Pentazocine did not make the cell membrane leaky through cellular damage because there was no increase in the efflux of the cytoplasmic enzyme LDH during pentazocine stimulation (Mizobe et al 1984). Therefore, pentazocine probably induced catecholamine efflux by a non-exocytotic mechanism.

In conclusion, pentazocine acts directly on the adrenal medulla to induce catecholamine efflux. This action of pentazocine would not be mediated by the opiate receptors, or result from potentiation of the physiological stimulus-secretion coupling in chromaffin cells. A non-exocytotic mechanism would be involved in the action of pentazocine.

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