abnormally low c.s.f. 5-HIAA values were elevated in a dose-dependent manner after clonazepam therapy.

The significance of our observations in relation to the etiology and treatment of human epilepsy remains to be elucidated.

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α_2-Adrenoceptors modulating diarrhoea in morphine-dependent rats

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Clonidine inhibits some naloxone-precipitated abstinence signs such as body shakes (Tseng et al 1975: Fielding et al 1978) and diarrhoea (Sparber & Meyer 1978) in several species, and nalorphine-elicited shaking behaviour in morphine-dependent rats (Vetulani & Bednarczyk 1977). The mechanisms by which clonidine reduced the morphine-abstinence syndrome are unknown. Atlas & Sabol (1980) suggested a possible close structural relationship between the ligand binding sites of α_2-adrenoceptors and opiate receptors. The inhibitory effects of clonidine on abstinence signs, however, were not antagonized by a narcotic antagonist naloxone (Tseng et al 1975; Sparber & Meyer 1978) or nalorphine (Vetulani & Bednarczyk 1977), which suggests a mechanism of action unlike that of narcotics. The pharmacological effects of clonidine are most commonly interpreted as reflecting an effect on α_2-adrenoceptors (Berthelsen & Pettinger 1977). There have been no reports which show directly in vivo that the inhibitory effects of clonidine on naloxone-precipitated abstinence signs are related to specific receptors. Therefore, we investigated effects of α-adrenoceptor agents to further characterize the type of receptors involved in the inhibitory effects of clonidine on naloxone-precipitated diarrhoea.

Male Wistar rats, 250–350 g, were cannulated into the right jugular vein under light ether anaesthesia and were subjected to continuous intravenous infusion of morphine or 0·9% NaCl (saline) at a rate of 4 mg kg^{-1} h^{-1} for 48 h as described previously (Nakaki et al 1980) using a modification of the method of Cox et al (1968). Immediately after the cessation of infusion, an α-adrenoceptor agonist or saline was injected subcutaneously. Naloxone (5 mg kg^{-1} s.c.) with or without an α-adrenoceptor antagonist (s.c.) was injected 30 min after the cessation of infusion. Diarrhoea was observed for 4 h after the naloxone challenge. Diarrhoea was defined as: expulsion of soft wet faeces which did not possess or retain a pellet shape. The statistical analyses were done by Fisher's exact test (Rimm et al 1980).

The following drugs were used: morphine HCl (Sankyo Co. Ltd., Tokyo, Japan), naloxone HCl (Endo

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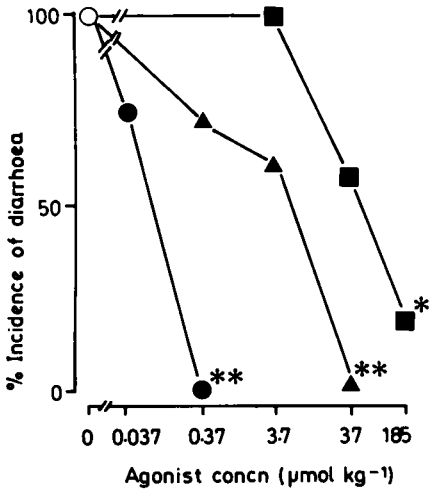

FIG. 1. Effect of various α-adrenoceptor stimulants on the naloxone-precipitated diarrhoea in morphine-dependent rats. Morphine was infused continuously (4 mg kg^{-1} h^{-1} i.v.) into the rats for 48 h. At the end of infusion, an α-adrenoceptor stimulant was injected subcutaneously, and, 30 min later, naloxone (5 mg kg^{-1} s.c.) was injected. Occurrence of diarrhoea was observed for 4 h after the naloxone challenge. Each point was obtained from 5 to 8 rats. ●: clonidine, ▲: α-methylnoradrenaline, ■: methoxamine. *: $P < 0.05$ vs 0 μmol kg^{-1} of the agonist. **: $P < 0.01$ vs 0 μmol kg^{-1} of the agonist.

Labs. Inc., N.Y., USA), yohimbine HCl (Nakarai Chemicals Co., Kyoto, Japan), prazosin HCl (Taito-Pfizer Co., Tokyo, Japan), clonidine HCl (C. H. Boehringer Sohn Ingelheim am Rhein, W. Germany), methoxamine HCl (Nippon Shinyaku Co., Ltd., Kyoto, Japan), and α-methylnoradrenaline HCl (Sterling-Winthrop Research Institute, Rensselaer, N.Y., USA).

None of the saline-infused rats showed diarrhoea after the naloxone challenge (data not shown). All the morphine-infused rats showed diarrhoea after naloxone injection without α-adrenoceptor agonists. Clonidine inhibited effectively the naloxone-precipitated diarrhoea in a dose-dependent manner, whereas methoxamine showed an only weak effect (Fig. 1). α-Methylnoradrenaline was intermediate between the two agonists. Clonidine was about 1000-fold more potent than methoxamine. Yohimbine reversed the inhibitory effect of clonidine on the naloxone-precipitated diarrhoea in a dose-dependent manner, whereas prazosin did not, even at 128 μmol kg^{-1} (= 53·5 mg kg^{-1}) (Table 1). The occurrence of diarrhoea was not due to the effect of yohimbine itself, since the drug alone did not cause diarrhoea in either morphine-dependent (Table 1) or naive rats (data not shown).

Clonidine and α-methylnoradrenaline are α_2-selective agonists, while methoxamine is α_1-selective (Berthelsen & Pettinger 1977). Yohimbine and prazosin are α_2- and

Table 1. Effects of yohimbine or prazosin on the inhibitory effect of clonidine on the naloxone-precipitated diarrhoea in morphine-dependent rats. Morphine was infused continuously (4 mg kg^{-1} h^{-1} i.v.) into the rats for 48 h. At the end of infusion, clonidine (0·37 μmol kg^{-1} s.c.) or saline (5 ml kg^{-1} was injected, and, 30 min later, naloxone (5 mg kg^{-1} s.c.) with saline, yohimbine or prazosin was injected subcutaneously. Occurrence of diarrhoea was observed for 4 h after the naloxone challenge. SAL: Saline; YOH: yohimbine; CLO: clonidine; NX: naloxone; PRA: prazosin.

Treatments	Dose of YOH or PRA (μmol kg^{-1})	Rats exhibiting diarrhoea
SAL + SAL + YOH	12·8	0/6
CLO + NX + SAL	0	0/6
CLO + NX + YOH	2·6	2/6
CLO + NX + YOH	12·8	6/6*
CLO + NX + PRA	12·8	0/4
CLO + NX + PRA	128	0/6

* $P < 0.01$ vs all the groups except CLO + NX + YOH (2·6 μmol kg^{-1}), Fisher's exact test.

α_1-selective antagonists, respectively (Tanaka & Starke 1979). Thus the results here implicate the involvement of α_2-adrenoceptors in the inhibition of naloxone-precipitated diarrhoea. The site of action of α-agonists here is still unknown. Aghajanian (1978) suggested that α_2-adrenoceptors and opiate receptors in the locus coeruleus regulate the opiate withdrawal syndrome. On the other hand, extra-brain tissues are possibly responsible for the inhibitory effects of α-agonists on diarrhoea. The guinea-pig ileum contains α_2-adrenoceptors (Drew 1978). The findings were further supported by the binding study of Tanaka & Starke (1979). It is probable, therefore, that the activation of the α_2-adrenoceptors results in the inhibition of acetylcholine release, so that the contractile response to cholinergic nerve stimulation decreases and in turn diarrhoea may be prevented, although the species difference between the guinea-pig and the rat should be considered.

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Effect of carnitine on heart alterations caused by tricyclic antidepressants

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Overdoses of tricyclic antidepressant drugs (TAD) may cause a number of adverse reactions among which cardiac arrhythmias are fairly frequent (Barnes et al 1968; Coull et al 1970; Jefferson 1975). Pyridostigmine β-adrenoceptor blocking agents and lignocaine are not completely satisfactory in the management of these disturbances (Torchiana et al 1972).

The observation that carnitine, a factor involved in the transfer of fatty acids across membrane (Fritz & Marquis 1965), beneficially influences some cardiac functions (Folts et al 1976; Vick et al 1976; Brook et al 1977) suggested we investigate whether this compound might in some way counteract the cardiac damage induced by TAD.

Materials and methods

Male New Zealand white rabbits, 2·5–3 kg, were anaesthetized with ethylurethane 1·2 g kg^{-1}. Nortriptyline hydrochloride (0·18 mg kg^{-1} min^{-1} (kindly supplied by Recordati, Milan, Italy) and (±)-carnitine hydrochloride (10 mg kg^{-1} min^{-1}, kindly supplied by SigmaTau, Pomezia, Italy), were infused into the marginal veins of respectively the right and the left ears. Each infusion lasted 40 min. When both compounds were given, carnitine infusion began 20 min before that of nortriptyline. Blood was withdrawn from the artery of the left ear at the beginning of the experiment, before starting nortryptiline infusion. E.c.g.s were traced by a Grass electrocardiograph. Standard limb connections were made with subcutaneous needle electrodes, lead II being mainly used for quantifying PQ and QRS intervals, which were measured with the help of a magnifying loop. At the end of the infusion, plasma and heart were collected and frozen. Nortriptyline was determined according to Bailey & Jatlow (1976) and (±)-carnitine according to Seccombe et al (1978). Statistical differences were evaluated by two-way analysis of variance and Tukey's test.

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Results and conclusions

Nortriptyline infusion caused a number of e.c.g. alterations. As shown in Table 1, PQ and QRS intervals progressively widened; at the end of infusion the PQ wave was virtually unmeasurable, and voltage waves were increased by about 100% in all the rabbits given nortryptiline. Episodes of ventricular tachycardia and bundle branch block were noted in 5 out of 8 rabbits.

Carnitine infusion itself did not result in modification of the e.c.g., but it delayed the widening of the PQ and QRS intervals caused by nortriptyline, and PQ intervals

Table 1. Effect of carnitine on e.c.g. abnormalities caused by nortriptyline.

	E.c.g. parameters					
	PQ ms ± s.e.			QRS ms ± s.e.		
Time (min)	Car.	Nort.	Car. + Nort.	Car.	Nort.	Car. + Nort.
Baseline	68 ± 2·0	59·8 ± 3·5	61·3 ± 1·9	28 ± 1	34·4 ± 1·1	33·5 ± 0·5
25	73 ± 1·5	63·6 ± 3·5	62·0 ± 1·8	28 ± 0·6	37·4 ± 1·2	34·8 ± 0·7
30	—	66 ± 3·5	62·0 ± 1·8	—	41·3 ± 1·3	36·7 ± 1·2
35	—	69·8 ± 2·8	63·6 ± 2·1	—	43·7 ± 1·3	38·2 ± 1·4
40	68·5 ± 2·0	78·2 ± 5·2	64·3 ± 1·8	29 ± 1	46·1 ± 1·6	41·2 ± 1·2
50	—	n.d.	66·1 ± 2·0	—	51·6 ± 1·9	41·5 ± 1·8
50	68·5 ± 2·0	n.d.	67·7 ± 2·2	28 ± 1·2	54·7 ± 1·9	45·2 ± 1·8

Car. = (±)-Carnitine HCl = 10 mg kg^{-1} min^{-1} × 40 min.
Nort. = Nortriptyline HCl = 0·18 mg kg^{-1} min^{-1} × 40 min.
Means of 8 rabbits ± standard error.