gastric mucosal barrier, which is considered of major importance in the gastric damage induced by aspirin.

Parsalmide also prevented gastric damage induced by other NSAIAs (Carminati et al 1981). Antagonism of experimentally induced ulcers has already been reported for anti-inflammatory drugs other than parsalmide (Robert et al 1977; Seegers et al 1978). The mechanism of action of this protection is not well understood. On the basis of our experiments, we can only speculate on the mechanisms by which parsalmide may prevent the effects of aspirin. It is likely that the strengthening of the mucosal barrier depends on some intrinsic property of parsalmide functioning at the level of the gastric mucosa. Recent results suggest that parsalmide is able to increase the production of gastric mucus in the rat (Bertaccini et al 1979) and gastric mucus is known to be essential for the protection of gastric mucosa (Allen & Garner 1980). Therefore, this property of parsalmide could at least partially account for its beneficial effects.

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Modulation of central noradrenaline release by postsynaptic receptors

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The release of noradrenaline (NA) from nerve terminals, in addition to being dependent on nerve impulses, is modified by α-adrenoceptors (Langer 1977; Starke 1979; Doxey & Roach 1980). In comparison with studies in the autonomic nervous system, studies in the c.n.s. are more difficult to interpret as there is no easily measurable equivalent to 'end-organ response'. The relative contributions of pre- and post synaptic components of drug action, therefore, are difficult to assess. By use of selective α-adrenoceptor agonists and antagonists, it has become apparent that there is some degree of α-adrenoceptor modulation of NA release in the c.n.s. (Anden et al 1967; Haggendal 1973; Meek & Neff 1973; Farnebo & Hamberger 1973; Braestrup & Nielsen 1976; Starke 1979). In contrast to the autonomic system, however, where the α-adrenoceptors modulating release are generally considered to be located presynaptically, the location of these receptors in the c.n.s. is more equivocal. In both systems the results obtained using selective antagonists at α_2-adrenoceptors such as yohimbine and rauwolscine, are generally considered as evidence indicative of a presynaptic locus (Langer 1977; Starke 1979; Doxey & Roach 1980). This has been substantiated by examining regulation of release from cell cultures containing no postsynaptic material and from synapses with no well-defined postsynaptic α-adrenoceptors (for review see Langer 1979). Certain anomalies (Kalsner & Chan 1979; Chan & Kalsner 1979) led (Kalsner et al 1980) to suggest that this hypothesis is too simplistic. It may be necessary, therefore, to re-examine the original suggestion that postsynaptic α-adrenoceptors may also modulate NA release (Haggendal 1970; Hedqvist 1970; Farnebo & Hamberger 1971; Farnebo & Malmfors 1971). This is of particular relevance in the c.n.s. where the location of receptors is less well defined than in the autonomic system. Using two selective postsynaptic α-adrenoceptor antagonists; prazosin (Doxey & Everitt 1977; Drew 1977) and indoramin (Rhodes & Waterfall 1978), we have attempted to examine the α-adrenoceptor mediated control of NA release in the c.n.s.

Synaptosomes were isolated from rat cerebral cortex using differential and density-gradient centrifugation (Gilbert & Wyllie 1976). Uptake was measured in a medium of the following composition (mM): NaCl 136; KCl 5; $MgCl_2$ 1·2; $CaCl_2$ 2·5; Tris 20; ascorbate 1; and glucose 10. The medium was gassed with pure oxygen and then adjusted to pH 7·4 with HCl. Uptake was initiated by addition of (−)-[^{3}H]NA[10^{-7} M], and terminated by filtration (Sugden 1974) on cellulose acetate 0·45 μm filters. All other analyses were as described elsewhere (Gilbert & Wyllie 1980; Wyllie & Gilbert 1980).

Treatment of animals with indoramin (5, 25 mg kg^{-1} orally) or prazosin (12·5, 62·5 mg kg^{-1} orally) reduced NA levels in 4 brain areas 2 h after dosing (Table 1).

* Correspondence.

Higher doses outside the normal therapeutic range of indoramin increased NA levels, an effect probably related to the sedative effects of the drug. The reduction in NA levels at lower doses of indoramin was secondary to an increased NA turnover; the rate of disappearance of NA in the presence of the synthesis inhibitor, α-methyl-*p*-tyrosine (250 mg kg^{-1} i.p.) was greater in indoramin-treated than in control rats (Fig. 1). The increased turnover of NA could be explained on the basis of an increased release of NA from nerve terminals prepared from drug-treated animals (Table 2). In this study no alterations were found in the activity of monoamine oxidase.

A similar increase in central NA turnover, secondary to α-adrenoceptor blockade, has been described for other drugs, including prazosin (Anden et al 1967; Meek & Neff 1973; Haggendal 1973; Braestrup & Nielsen 1976; Starke 1979). The ability of indoramin and prazosin to produce a fall in NA levels depends both on an augmented NA release in the presence of these drugs and also on the blockade of NA re-uptake. Both indoramin and prazosin inhibited NA uptake into synaptosomes with IC50's (μM) of 1·3 and 9·8 respectively. An effect on release, independent of one on re-uptake (or vice versa), may not always result in

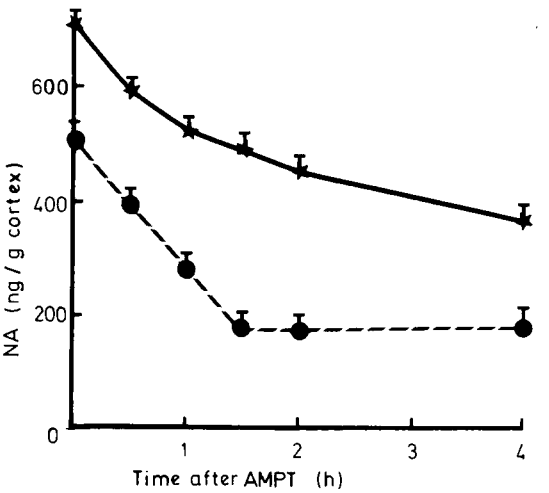

FIG. 1. The decline in rat cerebral cortex noradrenaline levels after injection with α-methyl-*p*-tyrosine (AMPT) (250 kg^{-1} i.p.). Animals were injected either with saline or indoramin (25 mg kg^{-1} i.m.) 2 hours before injection with AMPT. The upper line represents the decline in noradrenaline levels after saline injection, the lower after indoramin injection. All values are the mean ± s.e.m. of 4 experiments.

Table 1. Effects of indoramin and prazosin on rat brain noradrenaline levels. All values are the mean ± s.e. mean of 4 experiments.

Drug	Dose mg kg^{-1} oral	Brain area NA ng g^{-1} (wet weight) Cortex	Hypothalamus	Striatum	Mid-brain
None		649±20	1008±44	502±38	631±12
Indoramin	5	487±42**	650±93**	399±35	501±30**
	25	505±19**	695±44**	363±30**	488±21***
Prazosin	12·5	497±49*	849±97**	416±44	522±24**
	62·5	507±20**	645±35***	415±18*	499±37**

* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

Table 2. The effects of drugs on synaptosomal NA release. Synaptosomal release was measured into a modified Krebs solution. The parameters of electrical stimulation were 100 Hz, 10 v, 1 ms with biphasic pulses of alternating polarity. Drugs were either added to synaptosomes in vitro† or synaptosomes were prepared from drug-treated animals and release subsequently measured in vitro††.

Drug	Concn (M) or dose mg kg^{-1}	NA release (nmol NA 100 mg Pr^{-1} h^{-1}) Basal	Electrically stimulated
None	—	22·4±1·7 (4)	76·5±2·3 (4)
In Vitro†			
Indoramin	10^{-5}	25·3±3·2 (4)	75·6±2·3 (4)
	10^{-6}	24·3±2·8 (4)	76·7±2·4 (4)
Prazosin	10^{-5}	27·2±2·4 (3)	81·6±2·9 (3)
	10^{-6}	24·1±2·3 (3)	29·4±4·3 (3)
Yohimbine	10^{-6}	32·8±2·6 (4)**	132·6±3·6 (4)***
In vivo††			
Saline	0·9% (2 ml kg^{-1})	23·8±2·9 (4)	78·4±2·8 (4)
Indoramin	25	32·9±1·4 (4)**	123·5±3·1 (4)***
Prazosin	12·5	30·6±1·6 (4)*	120·6±2·4 (4)**

Number of experiments are given in parentheses.
* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

alterations in turnover of sufficient magnitude to reduce NA levels. In the heart, for example, phenoxybenzamine, which inhibits NA uptake and blocks the postsynaptic α-adrenoceptors but not re-uptake, does not decrease levels (Fillenz & Howe 1975). Phentolamine in the presence of an uptake inhibitor, however, reduces NA levels (Dorris & Shore 1976).

Surprisingly, however, neither indoramin nor prazosin increased basal or electrically-stimulated release of NA in vitro (Table 2). Synaptosomal preparations, containing essentially presynaptic material, did respond to the presynaptic α-adrenoceptor antagonist yohimbine. These results show that indoramin and prazosin, unlike yohimbine, do not stimulate either directly or indirectly the release of NA in vitro. This was in marked contrast to the augmented release of NA from synaptosomes prepared from drug-treated animals. Taking this and the drugs' known specificity for the postsynaptic receptor into account (Doxey & Everitt 1977; Drew 1977; Rhodes & Waterfall 1978), it would seem that their effects on NA release in vivo were probably not mediated by an action on presynaptic receptors or were secondary to drug redistribution during the isolation procedure. Whatever mechanism is involved, it must be rapid in onset as the effects are observed 1–4 h after drug treatment. One explanation is that there is transynaptic regulation of noradrenaline release not involving presynaptic α-receptors.

Although a postsynaptic site for the control of release has been largely dismissed (Langer 1977; Starke 1979; Doxey & Roach 1980), the bulk of evidence has been accumulated from experiments involving the autonomic system and there are many anomalies (Kalsner & Chan 1979; Chan & Kalsner 1979; Kalsner et al 1980). The effects of indoramin and prazosin on release are unlikely to be linked directly to the receptors involved in the initiation of a response in the effector cell. Assuming transynaptic regulation exists there could be, however, a more indirect association with a feedback mechanism mediated via some humoral agent. Candidates for this role would include prostaglandins of the E series which are known to inhibit NA release and to be formed postsynaptically (Hedqvist 1973; Gilmore et al 1968) in response to the activation of α-adrenoceptors (Hedqvist 1973). These results, however, do not preclude the existence of neuronal feedback through multi-synaptic pathways or other mechanisms.

Finally it is pertinent to note that prazosin, the archetypal selective postsynaptic α-adrenoceptor antagonist (Langer 1979), has similar effects on NA turnover in rat heart (Fuller et al 1978), a species considered to display normal selective prazosin antagonism of postsynaptic receptors (Cavero et al 1977). This must raise the possibility that postsynaptic control of NA release may also be apparent in the autonomic system. The receptors involved would not necessarily be those associated with end-organ response. These findings suggest that, in addition to the established presynaptic mechanisms, processes mediated by the action of NA at the postsynaptic membrane may be important in the modulation of the release of NA from nerve endings.

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