shown are the potencies of these compounds as sedatives relative to clonidine as assessed by oral dosing in mice (rota-rod test, locomotor activity, fall in body temperature). It is apparent that in this series of compounds there is a separation between the sedative and hypotensive activity in some of the analogues. For instance ICI 101187 was as potent as clonidine in lowering BP while it was only 1/10 as active as a sedative, whereas ICI 109683 and ICI 110802 were less active than ICI 101187 in lowering BP but were about twice as potent as sedatives, although still less sedative than clonidine. ICI 106270 was slightly less potent than clonidine in lowering BP, but was only about 1/80 as potent as a sedative.

When given intravenously to conscious renal hypertensive dogs at a dose of clonidine (10 μg/kg) ICI 101187 and ICI 106270 produced initial BP increases then prolonged falls in BP of $-29 \pm 3/-26 \pm 2$ mmHg ($n = 6$) with clonidine, $-26 \pm 3/-26 \pm 3$ mmHg ($n = 7$) with ICI 101187, and with ICI 106270 the fall in BP was $-23 \pm 4/-13 \pm 3$ mmHg ($n = 7$). Given orally at a dose of 250 μg/kg to conscious renal hypertensive dogs clonidine, ICI 101187, and ICI 106270 produced falls in BP of $-23 \pm 6/-26 \pm 6$ mmHg ($n = 5$), $-19 \pm 5/-23 \pm 2$ mmHg ($n = 5$) and $-18 \pm 6/-13 \pm 6$ mmHg ($n = 3$) respectively. These falls in BP were of about 5h duration. Dogs were prepared with a cannula in a lateral ventricle to allow administration of compounds directly into the CSF of conscious animals and doses of as low as 1 μg/kg of clonidine, ICI 101187 and ICI 106270 produced falls in BP of 20 mmHg.

In chloralose anaesthetized cats sympathetic efferent activity is reduced by all three compounds whether they were administered centrally or intravenously. Further CNS testing of both ICI 101187 and ICI 106270 has confirmed that the sedative potential of these compounds is much lower than that of clonidine.

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Changes in tyrosine hydroxylase and phenylethanolamine N-methyl transferase activity in individual brain nuclei during the development of renovascular hypertension in the rat

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In the early stages of renovascular hypertension, as blood pressure rises, there is a transient reduction in noradrenaline concentration of certain brain nuclei (Petty & Reid, 1977). To determine whether this initial fall in tissue noradrenaline reflects increased or decreased neuronal activity, we have measured the activity of the rate-limiting enzyme tyrosine hydroxylase (TH) by a modification of the method of Shiman, Akino & Kaufman (1971) in the same brain nuclei. Phenylethanolamine-N-methyl transferase (PNMT) activity has also been measured in these areas, since Saavedra, Grobecker & Axelrod (1976) reported that PNMT was increased in some regions of brainstem in spontaneous and mineralocorticoid hypertension.

Hypertension was produced in male Wistar rats by applying a silver clip to the left renal artery, and contralateral nephrectomy (the one kidney Goldblatt model). Animals were decapitated after 3, 7 and 28 days, and brain nuclei removed by the microdissection technique of Palkovits (1973). At 3 days after operation, TH activity was higher in the nucleus of the solitary tract, and the parahypoglossal nucleus, when compared to sham operated litter mates, whereas in the hypothalamus there was a significant reduction in the periventricular ($P < 0.05$), paraventricular ($P < 0.01$) and posterior hypothalamic ($P < 0.05$) nuclei. There were no changes in PNMT activity at this time. Seven days after operation, there was no difference between the levels of TH in clipped and sham operated animals. PNMT activity was now significantly increased in the nucleus of the solitary tract (14.6 ± 2.2, 7.4 ± 1.2 nmol/mg protein/h in hypertensive and control groups, $P < 0.05$). There was no difference in TH levels 28 days after operation but PNMT activity was higher in the brainstem regions of hypertensive animals (nucleus of the solitary tract ($P < 0.01$), parahypoglossal nucleus ($P < 0.05$), locus coeruleus ($P < 0.05$), cerebellar cortex ($P < 0.02$)). At no time was a change in PNMT observed in the hypothalamic nuclei.

The decrease in noradrenaline 3 days after opera-

tion (Petty & Reid, 1977) is thus accompanied by a decrease in tyrosine hydroxylase in the hypothalamic terminals, and an increase in the activity of this enzyme in the cell body regions of the brainstem. This could represent an increase in synthesis to compensate for an increase in noradrenergic neuronal activity. The elevation of PNMT activity at 7 and 28 days in the brainstem suggests that adrenaline formation in these neurones is increased during the development of renovascular hypertension. These studies support the hypothesis that during the development of renovascular hypertension there are localized increases in activity of noradrenaline and adrenaline containing neurones in the brain.

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Stimulus-response relationships in ileum preparations from normal and morphine treated guinea pigs

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The longitudinal muscle – myenteric plexus preparation from morphine pretreated guinea pigs shows reduced sensitivity to opiate induced inhibition of electrically stimulated acetylcholine release (Goldstein & Schulz, 1973). This reduction in opiate sensitivity is not associated with a change in opiate receptor binding properties (Cox & Padhya, 1977). Thus tolerance results from an alteration in neuronal function subsequent to the drug-receptor interaction, and may be reflected in general changes in neuronal properties. The relationship between the strength or duration of the electrical stimulus and the contractile response has therefore been examined in ileum preparations from untreated and 3 day morphine pretreated (Cox & Padhya, 1977) guinea pigs. Stimulus duration (ms)-response (tension generated, g) curves at constant voltage (80 V), or stimulus strength (V)-response curves at constant pulse duration (1 ms) were constructed in the absence of added drug, and in the presence of normorphine.

The normorphine concentration required to reduce by 50% the contractions elicited by 80 V, 0.25 ms stimuli was increased about three fold following morphine pretreatment. In preparations from both normal and morphine pretreated guinea pigs, stimuli of longer than 0.25 ms induced contractions that could not be completely inhibited by normorphine at a concentration (1 μM) approximately ten fold higher than its IC_{50} in normal preparations (Figure 1). No further inhibition could be obtained with higher normorphine concentrations. However, these residual contractions were completely inhibited by tetrodotoxin (300 nM) or by atropine (100 nM). The stimulus sensitivity and maximum tension generated by the opiate insensitive mechanism was not changed by morphine pretreatment (Figure 1).

In contrast, the normorphine suppressible component of the total response to electrical stimulation was consistently greater following morphine pretreatment (Figure 1). Under stimulus conditions giving maximum contractions, the opiate insensitive responses represented 44 ± 3% (n = 8) of the maximum responses in control preparations and 27 ± 4% (n= 8) in morphine pretreated preparations. Addition of normorphine (100 nM) to pretreated strips reduced the magnitude of the total response to a level comparable to that in control preparations (Figure 1).

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