The effect of acute doses of buprenorphine on concentrations of homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) in the rat forebrain

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The new narcotic antagonist analgesic, buprenorphine (0.01–1.0 mg/kg, s.c.), induces ipsilateral turning behaviour in rats with lesions (caused by 6-hydroxydopamine) in the left substantia nigra (Cowan, Dettmar & Walter, 1975a). Over the same dose range, buprenorphine antagonizes apomorphine-induced turning in the rat model (Cowan, Dettmar & Walter, 1975b). These effects may be related to an ability of buprenorphine to release dopamine in the central nervous system but an indirect action on noradrenergic or tryptaminergic pathways cannot be excluded. To investigate these possibilities, the concentrations of homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were simultaneously measured in the forebrains (containing frontal cortex, basal ganglia and hypothalamus) of male Sprague-Dawley albino rats (150–180 g; $n=5$–6) 1 h after injection of buprenorphine hydrochloride (0.1, 3 and 10 mg base/kg, s.c.), haloperidol (0.3, 1 and 3 mg/kg, i.p.), or vehicle (5 ml/kg).

5-Hydroxyindoleacetic acid was measured using the method of Curzon and Green (1970) and MHPG was estimated using a semi-micro method based on the gas-liquid chromatographic procedure of Walter & Eccleston (1973); HVA was estimated using gas liquid chromatography after forming the 4′-trifluoracetyl, trifluorethyl ester of HVA.

Statistically significant increases in the concentration of HVA were obtained after injection of buprenorphine (0.1, 3 and 10 mg/kg, $P<0.01$ by Student's t test) or haloperidol (0.3, 1 and 3 mg/kg, $P<0.01$) however, the concentrations of 5-HIAA and MHPG were not significantly affected by either compound.

Naloxone hydrochloride (3 mg salt/kg, s.c. at −5 min) antagonized the increase in HVA caused by buprenorphine (0.1 mg/kg, $P<0.05$; 3 mg/kg, $P<0.01$) but had no significant effect on the increase in HVA produced by haloperidol (1 mg/kg). At this dose level, naloxone did not significantly alter the concentrations of HVA, 5-HIAA or MHPG. The contrasting results obtained with naloxone are similar to the previous findings (Cowan, Dettmar & Walter, 1975b) that naloxone (3 mg/kg) antagonizes the inhibitory effect of buprenorphine (0.1 mg/kg), but not that of haloperidol (1 mg/kg), on apomorphine-induced turning behaviour in rats.

The present data suggest that doses of buprenorphine which cause behavioural changes may increase the turnover of dopamine, but not that of noradrenaline or 5-hydroxytryptamine, in the forebrain of rats. An opiate link would appear to be involved in the mediation of this effect since the rise in HVA is naloxone-sensitive.

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The stimulated release of dopamine-β-hydroxylase from intact organs of normo- and hypertensive rats

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Measurement of the circulating levels of dopamine-β-hydroxylase (DBH), the mixed function oxidase catalysing the hydroxylation of dopamine to noradrenaline in postganglionic monoaminergic neurones and the adrenal medulla, has been proposed as a useful index of sympathetic nervous activity (Axelrod, 1972). Its application as a means of studying sympathetic nervous involvement in hypertension has not been accepted by all workers (Geffen, Rush, Louis & Doyle, 1973; Horwitz, Alexander, Lovenberg & Keiser, 1973) since the enzyme levels measured in serum from man and

animals cannot be consistently shown to correlate with blood pressure changes as a result of increased sympathetic activity. However, raised circulating levels of DBH have been observed in certain types of hypertension in man and animals (De Champlain, Farley, Cousineau & van Ameringen, 1976; Schanberg & Kirshner, 1976).

Circulating DBH is believed to be derived from monoaminergic nerve-endings of all sympathetically innervated tissues, therefore estimation of DBH in the circulation is not a satisfactory measurement of the stimulated release of neuronal DBH. An alternative is described below.

Experiments were performed on female rats (C.F.E. derived strain) weighing 200–240 grams. The animals were prepared for stimulation of the sympathetic outflow using a modification of the Gillespie and Muir preparation (1967) and artificially respired. The splenic vein of eight rats was cannulated and connected to a cannula in the left femoral vein to maintain haemodynamic continuity. The hepatic-portal vein of a further eight rats was cannulated and similarly connected to a femoral vein cannula. The blood pressure was monitored in all animals by means of a cannula placed in the left carotid artery. Blood samples were collected from the spleen or hepatic-portal vein following selective stimulation of the sympathetic outflow supplying the coeliac and superior mesenteric ganglia (T10-L1), at frequencies between 1 and 25 Hz (20 V, pulse-width 0.3 ms for 5 s). At the same time blood samples were taken from the carotid artery to serve as controls. DBH released from heart tissue was measured by sampling from the aortic arch of eight rats following selective stimulation at frequencies between 0.5 and 5 Hz (30 V, pulse-width 0.5 ms for 15 s) of the spinal outflow to the stellate ganglion (C7-T1). Serum was removed simultaneously from the femoral vein to serve as a control. These experiments were repeated using various types of hypertensive rats. The animal models used were spontaneously hypertensive, renal hypertensive and deoxycorticosterone acetate/NaCl rats.

The serum was assayed for DBH activity by the spectrophotometric method of Kato, Kuzuya & Nagatsu (1974).

In each of the three tissues, DBH was shown to be released in a frequency dependent manner. The maximum enzyme levels released in response to stimulation expressed as $nmol.ml^{-1}.h^{-1} \pm$ s.e. mean, were spleen, 25.25 ± 2.25, (25 Hz); mesentery, 14.3 ± 0.95, (25 Hz); and heart 9.1 ± 1.7 (5 Hz). The stimulated release of the enzyme in hypertensive animals did not differ significantly from those of the normotensive rats.

These results provide further evidence for the combined release of DBH and noradrenaline at nerve endings. They also suggest that biochemical mechanisms associated with the release of transmitter at the sympathetic postganglionic nerve-ending do not differ significantly in hypertensive rats.

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Evidence for tryptamine receptors on cardiac sympathetic nerves

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5-Hydroxytryptamine (5-HT) stimulates noradrenaline release from rabbit cardiac sympathetic nerves (Fozard & Mwaluko, 1976). Despite the fact that classical tryptamine receptor antagonist drugs displayed no selective blocking activity, the possibility was considered that tryptamine receptors (Gaddum & Picarelli, 1957) exist on the terminal fibres which evoke transmitter release when activated (Fozard & Mwaluko, 1975). In an attempt to clarify the situation, the effects of several analogues of 5-HT have been investigated on the rabbit heart and comparisons have