The ability of local injection of 6-OHDA, 5,6-DHT and 5,7-DHT into the olfactory bulbs, to mimic the effects of bilateral bulbectomy in the rat

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Bilateral removal of the olfactory bulbs produces a behavioural syndrome in rats which cannot be attributed to loss of olfactory sensibility (van Riezen, Schnieden & Wren, 1977). We have attempted to simulate bulbectomy by local injections into the olfactory bulbs of various neurotoxic drugs.

Male Wistar rats (150–220 g) were subjected to bilateral olfactory bulbectomy or sham-operation under anaesthesia. Fourteen days after surgery, the rats were tested for passive avoidance and irritability (van Riezen, Schnieden & Wren, 1977). On the day following the behavioural tests the rats were subjected to a regular footshock stress (Basset, Cairncross & King, 1973) and plasma samples collected for assay of 11-hydroxycorticosterone by the method of Mattingly (1962).

These experiments were repeated with rats which had received bilateral intrabulbar injections of 6-OHDA (5 and 10 μg/2 μl vehicle), 5,6-dihydroxytryptamine (5,6-DHT; 4 and 8 μg/2 μl vehicle) and 5,7-dihydroxytryptamine (5,7-DHT; 4 and 8 μg/2 μl vehicle). Another group received 5,7-DHT (8 μg) 30 min after an intraperitoneal injection of desmethylimipramine (25 mg/kg).

When compared with sham-operated rats, bulbectomized animals produced an increase in the number of trials required to acquire the avoidance response, an increase in the irritability score and an elevation of plasma 11-hydroxycorticosterone concentrations after stress (Table 1). 5,6-DHT (4 μg) produced a similar increase in irritability scoring only, whereas the high dose produced a syndrome identical to that seen after bulbectomy. 5,7-DHT (4 μg) also produced a significant increase in the irritability score. In contrast the high dose of this analogue brought about no changes in behaviour or steroid levels. In conjunction with desmethylimipramine pretreatment however, 5,7-DHT (8 μg) produced the full syndrome. After injection of 6-OHDA (5 μg), rats required significantly more trials to reach the learning criterion but no part of the syndrome was seen after injection of 10 μg 6-OHDA.

Cryostat sections of fixed brains were stained according to the Hjorth-Simonsen (1970) modification of the Fink-Heimer (1967) method for silver impregnation and observed for signs of neuronal degeneration under light microscopy.

Table 1 Effects of bulbectomy and drug injections on behaviour and plasma 11-hydroxy-corticosterone (11-OHCS) concentrations in rats[1]

Treatment	*n*	*Passive avoidance*[2] *(No. of trails)*	*Irritability score*[2]	*Stress-induced [11-OHCS]*[2] *(μg/100 ml plasma)*
Bulbectomy	12	5.8 ± 0.3	6.8 ± 0.7	78.1 ± 3.04
Sham-operation	12	2.7 ± 0.4	1.7 ± 0.2	44.4 ± 3.04
Vehicle	6	3.6 ± 0.5	1.6 ± 0.4	42.1 ± 2.9
5,6-DHT 4 μg	9	3.8 ± 0.5	5.1 ± 0.4*	53.5 ± 2.2
5,6-DHT 8 μg	5	4.8 ± 0.4*	5.1 ± 0.8*	77.3 ± 4.3*
5,7-DHT 4 μg	3	3.0 ± 0.0	5.0 ± 1.0*	40.8 ± 7.6
5,7-DHT 8 μg	4	4.0 ± 0.4	2.0 ± 0.8	49.7 ± 5.7
5,7-DHT 8 μg + DMI (25 mg/kg)	6	5.8 ± 0.6*	4.5 ± 0.5	73.3 ± 5.0*
6-OHDA 5 μg	8	3.2 ± 1.0	2.2 ± 0.6	42.1 ± 2.04
6-OHDA 10 μg	10	4.0 ± 0.3	2.1 ± 0.3	44.4 ± 4.2

[1] Bulbectomy, sham-operation and bilateral injection into the olfactory bulbs (2 μl volumes of saline and ascorbic acid vehicle) were performed 14 days prior to testing.
[2] Results expressed as the mean and s.e. mean.
* Represents results which are not significantly different to those of bulbectomized rats.

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The xanthene-spiropiperidines: a new group of centrally-active drugs

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Any molecule which possesses a planar area (usually aromatic) and a nitrogen atom capable of occupying the same juxtaposition in space as the phenolic ring and the nitrogen of morphine can theoretically possess opiate properties. The Beckett and Casy model (Figure 1a) represents these requirements. From a variety of structures synthetized in a search for novel analgesic drugs, the xanthene-spiropiperidines of the general structure indicated in Figure 1(b) proved to be the most interesting. The similarity between the spiropiperidine moeity and morphine can be seen by comparison with Figure 1(c).

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The unsubstituted spiropiperidine (ICI 81,058: R and R_2=H; R_1=Me) is virtually devoid of opiate properties (activity relative to normoprhine = < 1% on the coaxially stimulated guinea pig ileum preparation [Paton (1957); Kosterlitz & Watt (1968)]), but is a potent sedative (54% decrease in locomotor activity of mice in photocell activity cages 1 h after 10 mg/kg p.o.) and antihistaminic (pA_2 v histamine on guinea pig ileum = 8.1). However, opiate properties are introduced when an hydroxyl is inserted at the 4 position (ICI 86,458: R=OH; R_1=Me; R_2=H). ICI 86, 458 has 16% of the potency of normorphine on the guinea pig ileum preparation and is analgesic (ED_{50} against acetic acid-induced writhing in mice = 1.3 mg/kg s.c.). The acetylated analogue (ICI 91,356: R=OAc; R_1=Me; R_2=H) is equipotent with normophine on the ileum and is a more effective analgesic (ED_{50} against acetic acid-induced writhing = 0.6 mg/kg s.c.).

Attempts to synthesize potent antagonists or partial agonists of the spiropiperidine series have met with little success e.g. the cyclopropylmethyl analogue (ICI 87,542: R=OH; R_1=CH_2-◁ ; R_2=H) has only 3% of the potency of naloxone on the mouse vas deferens preparation constantly perfused with etor-

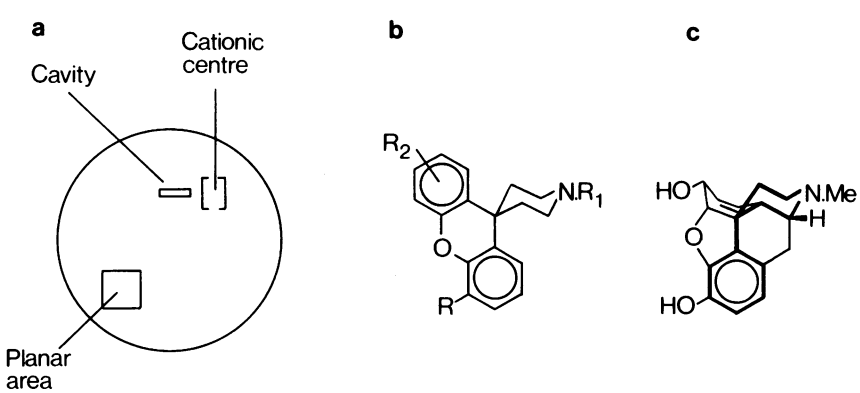

Figure 1 (a) Model of Beckett & Casy, 1954; (b) Spiropiperidine; (c) Morphine.