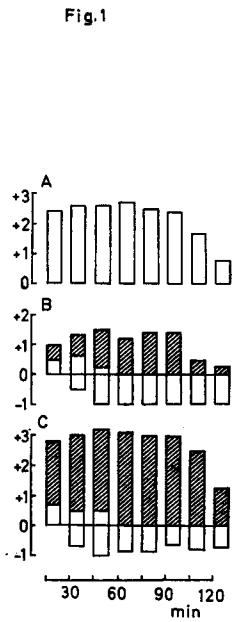
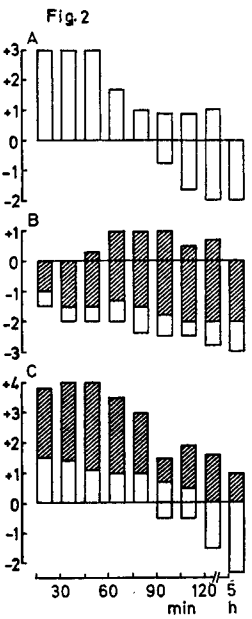
Serotonergic involvement with the stereotypy/catalepsy induced by morphine-like agents in the rat

The induction of stereotyped behaviour patterns is generally considered in terms of an enhancement of cerebral dopaminergic function whilst evidence suggests that cataleptic behaviour is the result of an inhibition of dopaminergic mechanisms (Fog, 1972). The opposing nature of these two behavioural states is emphasised by clinical observations that agents which cause stereotypy in animals are able to precipitate psychotic disturbances in man (amphetamine-type drugs) (Snyder, 1973) whilst agents which cause catalepsy are able to alleviate the symptoms of psychoses (neuroleptic agents). The spectrum of behavioural activity of morphine-like agents, especially that of the oripavine derivatives, would, therefore, appear surprising and certainly unique in that these agents are able to cause both catalepsy and stereotyped behaviour, the two behavioural states developing concurrently for some agents, for example, buprenorphine (M6029, *N*-(cyclopropylmethyl)-19-t-butyldihydronororvinol hydrochloride) and M6007 (*N*-(cyclopropylmethyl)-19-n-propyl-dihydronororvinol hydrochloride), such that an animal may maintain a cataleptic immobility whilst exhibiting stereotyped biting or licking responses (Costall & Naylor, 1974a).

Some explanation for this paradoxical situation has been provided by brain lesion studies which show a difference in the sites of action of the morphine-like drugs and the more classical stereotypic and cataleptic agents. Thus, lesions placed in the neo- or paleostriatum have been shown to reduce or abolish the cataleptic effect of the neuroleptic agents but such lesions potentiate the cataleptic action of morphine-like agents, although their stereotypic ability is abolished similarly to that of the dopamine agonists (Costall & Naylor, 1973; 1974a). Further, lesions placed in the central nucleus of the amygdala abolish the biting component of the stereotypic activity of many dopamine agonists but the stereotyped biting induced by the morphine-like agents is enhanced by these lesions, although their cataleptic effect is abolished in a manner similar to that of the neuroleptics (Costall & Naylor, 1974a, b, c). These observations have led to the hypothesis of an amygdaloid-cataleptic: striatal-stereotypic balance for the action of morphine-like agents in the rat (Costall & Naylor, 1974a). However, all considerations of the mechanisms involved with these behavioural effects have been almost exclusively in terms of dopamine mechanisms but recently the induction of stereotyped responses by dopamine agonists has been shown to depend on serotonergic (5-HT) as well as dopamine function (Costall & Naylor, 1974d). Since the two areas shown to be most important for the action of morphine and similar agents receive a significant 5-HT as well as dopaminergic innervation (Ungerstedt, 1971) it was considered that a 5-HT dopamine relation may also be important for the action of these agents.

This possibility was investigated by determining the effects of lesions placed in the medial or dorsal raphé nucleus on the catalepsy/stereotypy induced by morphine sulphate (BDH), M6029 and M320 (*N*-(cyclopropylmethyl)-19-isopentylnororvinol hydrochloride) (Reckitt and Colman). Lesions were induced in the raphé nuclei of male Sprague-Dawley rats as previously described (Costall & Naylor, 1974d). Briefly, lesions were induced by electrolytic coagulation (1·0 mA for 10 s) at Ant. 0·3, Vert. −2·6 (1·6), Lat. 0 (medial raphé nucleus) and Ant. 0·1, Vert. −0·8 (+0·2), Lat. 0 (dorsal raphé nucleus) (König & Klippel, 1963). Vertical coordinates for sham-operated animals are given in parentheses. Acute effects of the lesions were determined on the 2nd to 4th postoperative days and chronic effects on days 18 to 24. Morphine and M6029 were used in the injection form prepared by the manufacturers and M320 was prepared in a minimum quantity of hydrochloric acid made up to





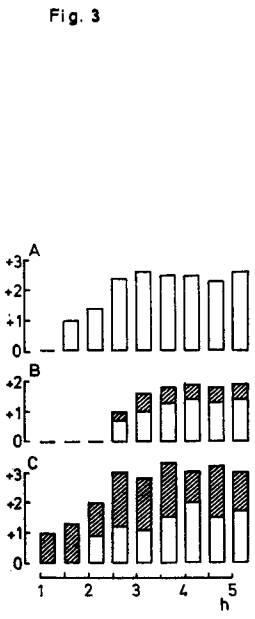


FIG. 1. Catalepsy (+ values) and stereotypy (— values) induced by 15 mg kg^{-1} morphine in A, normal rats and rats with B, lesion of the medial raphé nucleus or C, lesion of the dorsal raphé nucleus hatched areas during the acute stage (day 2–4) or open areas chronic stage (day 18–24), all values being with respect to zero. Similar observations were made at 20 and 40 mg kg^{-1} morphine. See Costall & Naylor (1974a) for dose-dependency of the morphine effect. Each value is the mean of at least 8 determinations. Standard errors are less than 15% of the means.

FIG. 2. Catalepsy (+ values) and stereotypy (— values) induced by 0·5 mg kg^{-1} M6029 in A, normal rats and rats with B, lesion of the medial raphé nucleus or C, lesion of the dorsal raphé nucleus hatched areas during the acute stage (day 2–4) or open areas chronic stage (day 18–24), all values being with respect to zero. Similar observations were made at 1·0 and 2·0 mg kg^{-1} M6029. See Costall & Naylor (1974a) for dose-dependency of the M6029 effect. Each value is the mean of at least 8 determinations. Standard errors are less than 12% of the means.

FIG. 3. Catalepsy (+ values) and stereotypy (— values) induced by 0·5 mg kg^{-1} M320 in A, normal rats and rats with B, lesion of the medial raphé nucleus or C, lesion of the dorsal raphé nucleus hatched areas during the acute stage (day 2–4) or open areas chronic stage (day 18–24), all values being with respect to zero. Similar observations were made at 1·0 and 2·0 mg kg^{-1} M320. See Costall & Naylor (1974a) for dose-dependency of the M320 effect. Each value is the mean of at least 8 determinations. Standard errors are less than 16% of the means.

volume with distilled water. All drugs were administered by the subcutaneous route in a volume of 1 ml kg^{-1}. Catalepsy was measured as the time an animal would maintain an imposed position with both front limbs extended over a 10 cm high bar. This was converted to a score such that 1 represents 0·1 to 2·5 min, 2 ≡ 2·6 to 5·0 min, 3 ≡ 5·1 to 10·0 min, 4 ≡ 10·1 to 20·0 min and 5 ≡ 20·1 min to ∞. Although the state of immobility induced by the morphine-like agents is frequently termed catatonia, this state is termed catalepsy in the present study for reasons previously stated (Costall & Naylor, 1974a). Stereotypy was scored such that 1 represents very periodic gnawing, biting or licking, periods of no stereotypy of duration 5 to 30 min, 2 ≡ periodic gnawing, biting or licking, periods of no stereotypy of duration 1 to 5 min, 3 ≡ continuous gnawing, biting or licking. Experimental conditions were as previously described (Costall & Naylor, 1974a).

In the chronic stage following both medial and dorsal raphé nucleus lesions the cataleptic effects of all agents were reduced and stereotypy became apparent with morphine and enhanced for M6029 (see Figs 1–3). The cataleptic phase of drug

action was similarly reduced in the acute stage following lesions of the medial raphé nucleus but an enhancement was recorded following dorsal raphé nucleus lesions (see Figs 1–3). However, this was associated with a marked enhancement of muscular rigidity with a slowness to correct the righting reflex and the results may reflect this rather than an increased cataleptic immobility. Similar, but lesser effects on rigidity were observed in sham-operated animals.

Results indicate an important role for 5-HT in the regulation of the behavioural effects of morphine-like agents and emphasize the difference in the mechanisms concerned with stereotyped behaviour induced by these agents and by the classical dopamine agonists (e.g. apomorphine, (+)-amphetamine) for, although both groups of drugs may mediate this behaviour, at least in part, via striatal dopaminergic mechanisms (striatal lesions reduce all forms of stereotypy and the dopamine blocking neuroleptic agents antagonize apomorphine and M6029 stereotypy in similar doses—Costall & Naylor, 1973; 1974b; unpublished observations), the relation to 5-HT may differ since lesions of the raphé nuclei enhance morphine-like stereotypy but reduce that of the dopamine agonists.

The present observations with raphé lesions virtually mimic those previously obtained for lesions of the nucleus amygdaloideus centralis when again stereotypy was enhanced whilst catalepsy was reduced or abolished. A possible conclusion must, therefore, be that the ability of the amygdaloid lesion to modify the stereotypic effect of morphine-like agents may be dependent upon interruption of its 5-HT mechanisms. The proposed amygdaloid-cataleptic: striatal-stereotypic balance may depend on 5-HT as well as dopamine mechanisms.

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REFERENCES

COSTALL, B. & NAYLOR, R. J. (1973). *Arzneimittel-Forsch.*, **23**, 674–683.
COSTALL, B. & NAYLOR, R. J. (1974a). *Psychopharmacologia* (Berl.), **35**, 203–213.
COSTALL, B. & NAYLOR, R. J. (1974b). *Adv. Neurol.*, in the press.
COSTALL, B. & NAYLOR, R. J. (1974c). *Eur. J. Pharmac.*, **25**, 138–146.
COSTALL, B. & NAYLOR, R. J. (1974d). *Ibid.*, in the press.
FOG, R. (1972). *Acta neurol. scand., Suppl.* 50, 1–66.
KONIG, J. F. R. & KLIPPEL, R. A. (1963). *The Rat Brain. A Stereotaxic Atlas of the Forebrain and Lower Parts of the Brain Stem.* Baltimore: The Williams and Wilkins Cppany.
SNYDER, S. G. (1973). *Am. J. Psychiat.*, **130**, 61–76.
UNGERSTEDT, U. (1971). *Acta physiol. scand., Suppl.* **367**, 1–48.