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THE EFFECTS OF ACUTELY ADMINISTERED ANALGESICS ON THE TURNOVER OF NORADRENALINE AND DOPAMINE IN VARIOUS REGIONS OF THE RAT BRAIN

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1 Noradrenaline and dopamine turnover rates were determined following blockade of synthesis by α-methyl-*p*-tyrosine. Morphine, pentazocine and methadone had no effect on steady state levels or on turnover of noradrenaline in whole brain and in the hypothalamus. Although morphine was without action on medulla-pons noradrenaline steady state levels, a drug-induced increase in turnover rate was observed which was antagonized by pretreatment with naloxone (5 mg/kg). Pentazocine and methadone failed to alter either the steady state level of noradrenaline in the medulla-pons or its turnover rate.

2 Morphine accelerated the decline in striatal α-methyl-*m*-tyramine levels following subcutaneous injection of α-methyl-*m*-tyrosine 18 h previously.

3 All three drugs increased the turnover of dopamine in whole brain and corpus striatum although the striatal effect was prevented by naloxone pretreatment. The minimum doses of morphine, pentazocine and methadone required to elicit a significant effect on striatal dopamine turnover were 10 mg/kg, 30 mg/kg and 10 mg/kg respectively.

4 The possibility of a dopaminergic involvement in the antinociceptive effect of analgesics is discussed.

Introduction

The observations that hypothalamic noradrenaline (NA) levels in the cat are decreased by acutely administered morphine (Vogt, 1954) and that pretreatment with reserpine diminishes the antinociceptive effect of morphine in mice (Schneider, 1954) have raised the possibility of central biogenic amines being implicated in the antinociceptive effect of the drug. Whilst it has been suggested that the antinociceptive action of morphine may be mediated via an adrenergic mechanism (Schneider, 1954; Takagi, Takashima & Kimura, 1964; Vedernikov & Afrikanov, 1969) there is also evidence implicating brain serotoninergic systems (Tenen, 1968; Samanin, Gumulka & Valzelli, 1970; Genovese, Zonta & Mantegazza, 1973). A study was therefore undertaken to investigate the effects of selected analgesics on the turnover of NA, dopamine and 5-hydroxytryptamine in the rat brain to determine whether they exerted similar effects on the turnover of all three amines. The results of the 5-hydroxytryptamine study will be presented elsewhere. The present investigation reveals that acutely administered morphine, methadone and pentazocine increase the turnover of dopamine in the rat corpus striatum; while morphine has no effect on NA turnover in whole rat brain or hypothalamus, a drug-induced increase in medullapons NA turnover was observed.

Preliminary accounts of some of these findings have been published (Sugrue, 1972, 1973).

Methods

Determination of rates of noradrenaline and dopamine synthesis

In all experiments, male Sprague-Dawley rats weighing 200-250 g were used. They were killed by a sharp blow on the head and the brain quickly removed. Following extraction (Neff & Costa, 1966), tissue levels of NA and dopamine were assayed by the trihydroxyindole fluorimetric procedure of Laverty & Taylor (1968).

Areas defined as hypothalamus (Sugrue, 1969), medulla-pons and corpus striatum (Glowinski & Iversen, 1966) were dissected from the remainder of the brain and freed from adhering tissue, material from 4 rats being pooled and weighed. In all experiments, NA and dopamine concentrations were calculated as μg amine/g wet tissue, results being corrected for 100% recovery.

Synthesis rates were determined by the method of Brodie, Costa, Dlabac, Neff & Smookler (1966) following blockade of synthesis by α-methyl-*p*-tyrosine (α-MPT) (200 mg/kg), injected intraperitoneally. Where time between injection and killing of the rats exceeded 2 h, a second dose of α-MPT (100 mg/kg) was injected intraperitoneally 3 h after the initial dose. Tissue NA and dopamine levels were logarithmically transformed for construction of regression lines by the method of least squares (Goldstein, 1964). The slope of the regression line was calculated and the amine loss rate constant (k) obtained from the equation: slope of the regression line equals 0.434 times k. The product of k and amine steady state levels yielded the rate of amine synthesis.

*Determination of α-methyl-*m*-tyramine levels*

α-Methyl-*m*-tyrosine (α-MMT) (100 mg/kg) was injected subcutaneously and rats killed at times stated in the results section. Striata from two rats were pooled and striatal α-methyl-*m*-tyramine (MMTA) concentrations measured (Shore & Alpers, 1964). Results were calculated as μg amine/g wet tissue, being corrected for 100% recovery.

Drugs and solutions

The following drugs were dissolved in 0.9% w/v NaCl solution (saline): morphine hydrochloride, methadone hydrochloride, naloxone hydrochloride, (±)-α-methyl-*m*-tyrosine methyl ester hydrochloride and (±)-α-methyl-*p*-tyrosine methyl ester hydrochloride. Pentazocine lactate was used in ampoule form (Fortral). Haloperidol was dissolved in 0.1 M citric acid. Unless stated otherwise, the intraperitoneal route was used. Controls received a similar volume of saline except in the case of haloperidol where the appropriate vehicle was used. Doses refer to the free base.

Results

Effect on rates of noradrenaline and dopamine synthesis in whole rat brain

Table 1 summarizes the results of experiments investigating the effect of morphine (20 mg/kg), pentazocine (60 mg/kg) and methadone (10 mg/kg) on both steady state levels and rates of synthesis of rat brain NA and dopamine. Steady state levels of NA and dopamine were unaltered

Table 1 Effect of morphine, pentazocine and methadone on the rates of synthesis of noradrenaline and dopamine in whole rat brain

Treatment	*Amine steady state levels (μg/g)*	*Slope*	*Amine loss rate constant*	*Synthesis rate ($\mu g\ g^{-1}\ h^{-1}$)*	*% change in synthesis rate*
Noradrenaline					
Control	0.440 ± 0.015	0.068	0.157	0.069	–
Morphine	0.432 ± 0.012	0.066	0.152	0.066	–4.3
Pentazocine	0.428 ± 0.011	0.065	0.150	0.065	–5.8
Methadone	0.414 ± 0.020	0.066	0.152	0.063	–8.7
Dopamine					
Control	1.030 ± 0.041	0.087	0.200	0.206	–
Morphine	1.101 ± 0.050	0.126**	0.290	0.319	+54.8
Pentazocine	1.000 ± 0.029	0.118*	0.272	0.272	+32.0
Methadone	0.966 ± 0.038	0.130**	0.299	0.289	+40.3

Morphine (20 mg/kg), pentazocine (60 mg/kg) and methadone (10 mg/kg) were injected i.p. 60 min prior to injection of α-MPT. α-MPT (200 mg/kg) was injected i.p. 1, 2, 4 or 6 h before the rats were killed. Where the time between injection and killing exceeded 2 h, a second dose of α-MPT (100 mg/kg) was injected i.p., 3 h after the initial dose. Each steady state value is the mean with s.e. mean of at least 6 observations. The number of values used to calculate the regression lines was at least twenty.
* $P < 0.05$; ** $P < 0.01$.

1 h after intraperitoneal injection of all three analgesics. None had any effect on rate of synthesis of rat brain NA. On the other hand, the exponential decline in rat brain dopamine following α-MPT was significantly increased by all three analgesics.

Effect on regional noradrenaline and dopamine rates of synthesis

Hypothalamic NA steady state levels at the time of α-MPT injection, together with the percentage amounts of NA remaining 2 and 4 h after α-MPT injection, were unaltered by morphine (20 mg/kg), pentazocine (60 mg/kg) and methadone (10 mg/kg) (Table 2).

Although morphine (20 mg/kg) had no significant effect on medulla-pons NA steady state levels at the time of α-MPT injection, a drug-induced increase of 33.7% in medulla-pons NA synthesis rate was observed (Table 3). Pretreatment with naloxone (5 mg/kg, i.p.) antagonized the ability of morphine (20 mg/kg) to effect a significant decrease in the percentage of medulla-pons NA remaining 2 h after α-MPT (Figure 1). Naloxone alone was devoid of effect in all experimental situations. Figure 1 also shows that the percentage of medulla-pons NA remaining 2 h after α-MPT was not significantly decreased by morphine (10 mg/kg). Both pentazocine (60 mg/kg) and methadone (10 mg/kg) had no significant action on medulla-pons NA steady state levels and, unlike morphine, elicited no significant change in synthesis rate (Table 3).

Table 3 shows that the regression coefficient, and hence the synthesis rate, for striatal dopamine was significantly increased by the administration of morphine (20 mg/kg), pentazocine (60 mg/kg) and methadone (10 mg/kg). Striatal dopamine steady state levels at the time of α-MPT injection

Table 2 Effect of morphine, pentazocine and methadone on α-methyl-*p*-tyrosine (α-MPT) induced falls in noradrenaline (NA) content of rat hypothalamus

Treatment	*Steady state NA levels (μg/g)*	*% NA remaining after α-MPT*	
		2 h	*4 h*
Control	1.79 ± 0.15	75.1 ± 2.1	60.3 ± 2.9
Morphine	1.76 ± 0.07	75.4 ± 3.3	60.2 ± 1.7
Pentazocine	1.59 ± 0.09	73.9 ± 3.6	58.9 ± 1.9
Methadone	1.66 ± 0.13	75.7 ± 3.7	57.8 ± 1.7

Morphine (20 mg/kg), pentazocine (60 mg/kg) and methadone (10 mg/kg) were injected i.p. 1 h prior to α-MPT. Rats were killed 2 or 4 h after initial α-MPT injection. Each value is the mean with s.e. mean of 5-8 observations.

Table 3 Effect of morphine, pentazocine and methadone on the rates of synthesis of rat striatal dopamine (DA) and medulla-pons noradrenaline (NA)

Treatment	*Amine steady state levels (μg/g)*	*Slope*	*Amine loss rate constant*	*Synthesis rate ($\mu g\ g^{-1}\ h^{-1}$)*	*% change in synthesis rate*
Striatal DA					
Control	5.74 ± 0.10	0.131	0.302	1.73	
Morphine	5.76 ± 0.08	0.165***	0.380	2.19	+26.6
Pentazocine	5.80 ± 0.08	0.154*	0.355	2.06	+19.1
Methadone	5.96 ± 0.12	0.159**	0.366	2.18	+26.0
Medulla-pons NA					
Control	0.551 ± 0.009	0.068	0.157	0.086	
Morphine	0.534 ± 0.010	0.094**	0.216	0.115	+33.7
Pentazocine	0.533 ± 0.008	0.074	0.170	0.091	+5.8
Methadone	0.553 ± 0.012	0.075	0.173	0.096	+11.6

Footnote as for Table 1.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

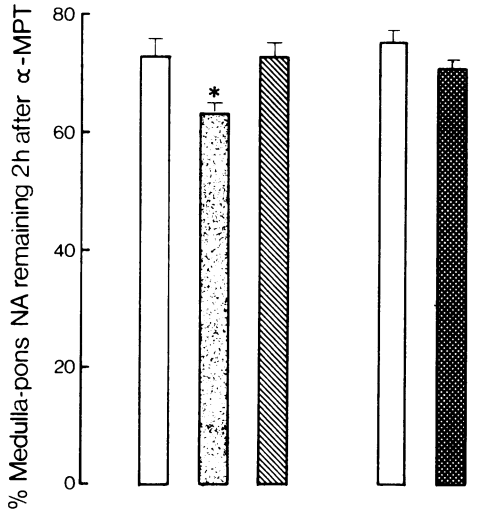

Fig. 1 Effect of morphine and naloxone plus morphine on the percentage of noradrenaline (NA) remaining in the rat medulla-pons 2 h after α-methyl-*p*-tyrosine (α-MPT). Morphine (20 mg/kg, stippled or 10 mg/kg, cross-hatched) was injected i.p. 1 h before the i.p. injection of α-MPT (200 mg/kg). Controls (open columns) received saline 1 h before α-MPT. Naloxone (5 mg/kg, diagonally hatched) was injected i.p. 15 min before morphine (20 mg/kg). Each column is the mean of 8 observations. Bars indicate s.e. mean. *$P < 0.01$.

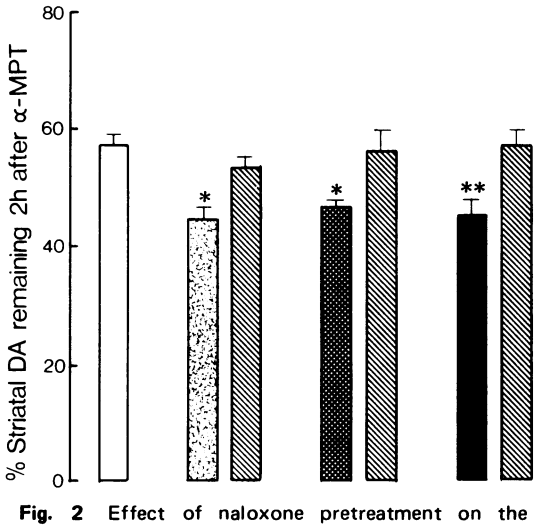

Fig. 2 Effect of naloxone pretreatment on the ability of morphine, pentazocine and methadone to decrease the percentage of dopamine (DA) remaining in the rat corpus striatum 2 h after α-methyl-*p*-tyrosine (α-MPT). Morphine (20 mg/kg, stippled), pentazocine (60 mg/kg, solid) or methadone (10 mg/kg, cross-hatched) were injected i.p. 1 h before the i.p. injection of α-MPT (200 mg/kg). Controls (open column) received saline 1 h prior to α-MPT. Naloxone (5 mg/kg, diagonally hatched) was injected i.p. 15 min before the analgesics. Each column is the mean of 8 observations. Bars indicate s.e. mean. * $P < 0.01$; ** $P < 0.001$.

were not significantly altered by any of the analgesics. The minimum doses of morphine, pentazocine and methadone necessary to decrease the percentage of striatal dopamine remaining 2 h after α-MPT significantly were 10 mg/kg, 30 mg/kg and 10 mg/kg respectively (Table 4). Pretreatment with naloxone (5 mg/kg) blocked the ability of morphine (20 mg/kg), pentazocine (60 mg/kg) and methadone (10 mg/kg) to effect a significant decrease in the percentage of striatal dopamine remaining 2 h after α-MPT administration (Figure 2).

Table 4 Effect of various doses of morphine, pentazocine and methadone on the percent amount of dopamine (DA) remaining in the rat corpus striatum 2 h after α-methyl-*p*-tyrosine (α-MPT) injection

Drug	*Dose (mg/kg)*	*% Striatal DA remaining*	
		Control	*Drug-treated*
Morphine	5	56.8 ± 1.9	53.8 ± 3.9
	10	56.7 ± 2.2	47.5 ± 1.8*
	20	58.4 ± 1.7	43.4 ± 2.1**
Pentazocine	15	59.0 ± 2.4	57.6 ± 2.3
	30	57.6 ± 1.9	47.4 ± 0.8*
	60	55.2 ± 2.2	46.9 ± 1.3*
Methadone	5	55.8 ± 2.0	52.3 ± 1.7
	10	57.0 ± 2.6	46.0 ± 2.6*

Morphine, pentazocine and methadone were injected i.p 1 h prior to α-MPT. Rats were killed 2 h after α-MPT injection. Each value is the mean with s.e. mean of 8 observations.
* $P < 0.01$; ** $P < 0.001$.

Table 5 Effect of morphine and haloperidol on striatal α-methyl-*m*-tyramine (MMTA) levels in the rat

Drug	Dose (mg/kg)	Striatal MMTA (μg/g) Control	Drug-treated	% Reduction
Morphine	20	0.355 ± 0.020	0.274 ± 0.013*	22.8
Haloperidol	1	0.342 ± 0.030	0.173 ± 0.024*	49.4

α-Methyl-*m*-tyrosine (100 mg/kg) was injected s.c. 18 h prior to the i.p. injection of either morphine or haloperidol and rats were killed 5 h after these injections. Each value is the mean with s.e. mean of 4-8 observations.
* $P < 0.01$.

*Effect on striatal α-methyl-*m*-tyramine levels*

Haloperidol (1 mg/kg) significantly lowered striatal MMTA levels and, while morphine (20 mg/kg) mimicked this effect, it should be noted that the dose employed was greater and the percentage change smaller (Table 5).

Discussion

The results of this study reveal that steady state levels of NA and dopamine either in whole rat brain or in selected brain regions were unaltered 1 h after the acute administration of morphine, pentazocine and methadone. The findings relating to pentazocine in this study do not agree with those of Holtzman & Jewett (1972) who observed significant reductions in rat brain NA and dopamine levels 0.5, 1 and 2 h after pentazocine (32 mg/kg, s.c.), although the reasons for this difference in results are not readily apparent.

Morphine, pentazocine and methadone, at the doses and time schedules employed, had no significant effect on rate of synthesis of NA in rat brain. The lack of effect of morphine on rat brain NA turnover has also been observed by Gunne, Jonsson & Fuxe (1969). These results are at variance with findings in other species. For example, mouse brain NA turnover is increased following acute administration of the drug (Smith, Sheldon, Bednarczyk & Villarreal, 1972). Moreover, Heinrich, Lichtensteiger & Langemann (1971) have demonstrated histochemically, in the mouse, that morphine affects both NA and dopamine central nerve cell bodies whereas only the substantia nigra dopaminergic system is altered in the rat. The reasons for these variations remain to be elucidated although it is well known that the behavioural effects of morphine vary with species, e.g. morphine excites mice and cats but depresses rats and dogs.

Although morphine had no effect on NA turnover in whole rat brain or hypothalamus, an increase in turnover was observed in the medulla-pons. The antagonism exerted by naloxone reveals that the increased turnover is a specific phenomenon. Of the three analgesics under study, only morphine altered medulla-pons NA turnover. Why morphine alone possesses this ability is not readily apparent although it is of interest to note that, while rat brain 5-hydroxytryptamine turnover is unaltered by both pentazocine and methadone, it is significantly increased by acute administration of moderate doses of morphine (Goodlet & Sugrue, 1972). Hence the effects of morphine on rat brain monoamine systems differ from those of pentazocine and methadone.

In this study, the property common to all three analgesics is their ability to increase turnover of dopamine both in whole rat brain and corpus striatum. Similar findings have recently been reported by others for morphine (Gunne *et al.*, 1969; Clouet & Ratner, 1970; Gauchy, Agid, Glowinski & Cheramy, 1973; Puri, Reddy & Lal, 1973; Kuschinsky, 1973) and methadone (Sasame, Perez-Cruet, Di Chiara, Tagliamonte, Tagliamonte & Gessa, 1972). Other groups of drugs such as the neuroleptics (Nyback & Sedvall, 1968) also increase rat striatal dopamine turnover. The question may therefore be asked whether the effect observed in this study with all three analgesics is specific or the result of some other action of the drugs such as their ability to give rise to catalepsy, a property possessed by both morphine and methadone (Smith, Lehman & Gilfillan, 1951). Evidence does not support the latter hypothesis. First, pentazocine does not evoke catalepsy (Ahtee & Kaariainen, 1973), yet it increases striatal dopamine turnover. Secondly, whereas pretreatment with naloxone antagonizes the ability of morphine, pentazocine and methadone to increase striatal dopamine turnover, it has no significant effect on the increase in striatal dopamine turnover evoked by haloperidol (unpub-

lished). This observation is in agreement with the findings of Kuschinsky & Hornykiewicz (1972) who observed that naloxone does not antagonize the increase in rat striatal homovanillic acid levels induced by chlorpromazine. Hence the ability of all three analgesics to augment striatal dopamine turnover would appear to be a specific phenomenon. Germane to the concept of a striatal-analgesic interaction is the reported presence of an opiate receptor in the rat corpus striatum (Pert & Snyder, 1973).

Dorris & Shore (1972) have postulated that MMTA acts as a false transmitter in dopaminergic neurones. As evidence for this hypothesis, they demonstrated that drugs regarded as capable of stimulating or blocking striatal dopamine receptors retarded or enhanced the decline in striatal MMTA levels respectively. The observation that morphine mimics haloperidol in regard to striatal MMTA changes suggests that the possible locus of action of morphine in the corpus striatum is post-synaptic. There is evidence to suggest that morphine blocks striatal dopamine receptors. For example, morphine prevents the stereotyped behaviour induced in rats by amphetamine and apomorphine (Puri *et al.*, 1973). On the other hand, the possibility that morphine may bring about a functional deficiency of dopamine in the striatum by diverting newly synthesized amine from storage sites to sites of catabolism, and thus possess a presynaptic site of action, has been proposed (Kuschinsky & Hornykiewicz, 1972; Wand, Kuschinsky & Sontag, 1973). The precise mechanism whereby analgesics increase striatal dopamine turnover awaits clarification.

To relate the antinociceptive effect of analgesics to striatal dopamine changes is both unwarranted and premature. However, the possibility of such a relationship should not be totally disregarded as recent findings suggest that dopamine may play a much more important central role than that previously envisaged. For example, dopaminergic neurones have been detected in the rat cerebral cortex (Blanc, Glowinski, Stinus & Thierry, 1973). Furthermore, the existence of a descending inhibitory pathway from the caudate nucleus to the sensory afferent system has been demonstrated and the possibility of the antinociceptive effect of morphine being mediated via an effect on such a system has been discussed (Fukui & Takagi, 1972). Finally, the observation in this study that not only morphine and methadone but also the partial agonist pentazocine affect rat striatal dopamine turnover in a similar manner lends credence to the concept of dopaminergic involvement in the antinociceptive effect of analgesics.

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References

AHTEE, L. & KAARIAINEN, I. (1973). The effect of narcotic analgesics on the homovanillic acid content of rat caudate nucleus. *Eur. J. Pharmac.*, **22**, 206-208.

BLANC, G., GLOWINSKI, J., STINUS, L. & THIERRY, A.M. (1973). Is cortical dopamine only the precursor of noradrenaline? *Br. J. Pharmac.*, **47**, 648P.

BRODIE, B.B., COSTA, E., DLABAC, A., NEFF, N.H. & SMOOKLER, H.H. (1966). Application of steady state kinetics to the estimation of synthesis rate and turnover time of tissue catecholamines. *J. Pharmac. exp. Ther.*, **154**, 493-498.

CLOUET, D.H. & RATNER, M. (1970). Catecholamine biosynthesis in brains of rats treated with morphine. *Science*, **168**, 854-856.

DORRIS, R.L. & SHORE, P.A. (1972). Evidence of α-methyl-*m*-tyramine as a false dopamine-like transmitter. *J. Pharm. Pharmac.*, **24**, 581-583.

FUKUI, K. & TAKAGI, H. (1972). Effect of morphine on the cerebral contents of metabolites of dopamine in normal and tolerant mice: its possible relation to analgesic action. *Br. J. Pharmac.*, **44**, 45-51.

GAUCHY, C., AGID, Y., GLOWINSKI, J. & CHERAMY, A. (1973). Acute effects of morphine on dopamine synthesis and release and tyrosine metabolism in the rat striatum. *Eur. J. Pharmac.*, **22**, 311-319.

GENOVESE, E., ZONTA, N. & MANTEGAZZA, P. (1973). Decreased antinociceptive activity of morphine in rats pretreated intraventricularly with 5,6-dihydroxytryptamine, a long-lasting selective depletor of brain serotonin. *Psychopharmacologia (Berl.)*, **32**, 359-364.

GLOWINSKI, J. & IVERSEN, L.L. (1966). Regional studies of catecholamines in the rat brain. I. The disposition of ^{3}H-norepinephrine, ^{3}H-dopamine, and ^{3}H-dopa in various regions of the brain. *J. Neurochem.*, **13**, 655-669.

GOLDSTEIN, A. (1964). *Biostatistics, an introductory text.* New York: The Macmillan Company.

GOODLET, I. & SUGRUE, M.F. (1972). Effects of acutely administered analgesic drugs on rat brain 5-hydroxytryptamine turnover. *Br. J. Pharmac.*, **46**, 562P-563P.

GUNNE, L.-M., JONSSON, J. & FUXE, K. (1969). Effects of morphine intoxication on brain catecholamine neurons. *Eur. J. Pharmac.*, **5**, 338-342.

HEINRICH, U., LICHTENSTEIGER, W. & LANGEMANN, H. (1971). Effect of morphine on the catecholamine content of midbrain nerve cell groups in rat and mouse. *J. Pharmac. exp. Ther.*, **179**, 259-267.

HOLTZMAN, S.G. & JEWETT, R.E. (1972). Some actions of pentazocine on behavior and brain monoamines in the rat. *J. Pharmac. exp. Ther.*, **181**, 346-356.

KUSCHINSKY, K. (1973). Evidence that morphine increases dopamine utilization in corpora striata of rats. *Experientia*, **29**, 1365-1366.

KUSCHINSKY, K. & HORNYKIEWICZ, O. (1972). Morphine catalepsy in the rat: relation to striatal dopamine metabolism. *Eur. J. Pharmac.*, **19**, 119-122.

LAVERTY, R. & TAYLOR, K.M. (1968). The fluorometric assay of catecholamines and related compounds: improvements and extensions to the hydroxyindole technique. *Analyt. Biochem.*, **22**, 269-279.

NEFF, N.H. & COSTA, E. (1966). The influence of monoamine oxidase inhibition on catecholamine synthesis. *Life Sci.*, **5**, 951-959.

NYBACK, H. & SEDVALL, G. (1968). Effect of chlorpromazine on accumulation and disappearance of catecholamines formed from tyrosine-C^{14} in brain. *J. Pharmac. exp. Ther.*, **162**, 294-301.

PERT, C.B. & SNYDER, S.H. (1973). Opiate receptor: demonstration in nervous tissue. *Science*, **179**, 1011-1014.

PURI, S.K., REDDY, C. & LAL, H. (1973). Blockade of central dopaminergic receptors by morphine: effect of haloperidol, apomorphine or benztropine. *Res. Comm. Chem. Path. Pharmac.*, **5**, 389-401.

SAMANIN, R., GUMULKA, W. & VALZELLI, L. (1970). Reduced effect of morphine in midbrain raphe lesioned rats. *Eur. J. Pharmac.*, **10**, 339-343.

SASAME, H.A., PEREZ-CRUET, J., DI CHIARA, G., TAGLIAMONTE, A., TAGLIAMONTE, P. & GESSA, G.L. (1972). Evidence that methadone blocks dopamine receptors in the brain. *J. Neurochem.*, **19**, 1953-1957.

SCHNEIDER, J.A. (1954). Reserpine antagonism of morphine analgesia in mice. *Proc. Soc. exp. Biol. Med.*, **87**, 614-615.

SHORE, P.A. & ALPERS, H.S. (1964). Fluorometric estimation of metaraminol and related compounds. *Life Sci.*, **3**, 551-554.

SMITH, C.C., LEHMAN, E.G. & GILFILLAN, J.L. (1951). Antagonistic action of N-allyl-normorphine upon the analgetic and toxic effects of morphine, methadone derivatives and isonipecaine. *Fed. Proc.*, **10**, 335.

SMITH, C.B., SHELDON, M.I., BEDNARCZYK, J.H. & VILLARREAL, J.E. (1972). Morphine-induced increases in the incorporation of ^{14}C-tyrosine into ^{14}C-dopamine and ^{14}C-norepinephrine in the mouse brain: antagonism by naloxone and tolerance. *J. Pharmac. exp. Ther.*, **180**, 547-557.

SUGRUE, M.F. (1969). A study of the role of noradrenaline in behavioural changes produced in the rat by psychotomimetic drugs. *Br. J. Pharmac.*, **35**, 243-252.

SUGRUE, M.F. (1972). Effects of morphine and pentazocine on rat brain noradrenaline and dopamine turnover. *Vth Int. Congr. Pharmac.*, p. 225.

SUGRUE, M.F. (1973). Effects of morphine and pentazocine on the turnover of noradrenaline and dopamine in various regions of the rat brain. *Br. J. Pharmac.*, **47**, 644P.

TAKAGI, H., TAKASHIMA, T. & KIMURA, K. (1964). Antagonism of the analgetic effect of morphine in mice by tetrabenazine and reserpine. *Arch. int. Pharmacodyn.*, **149**, 484-492.

TENEN, S.S. (1968). Antagonism of the analgesic effect of morphine and other drugs by *p*-chlorophenylalanine, a serotonin depletor. *Psychopharmacologia (Berl.)*, **12**, 278-285.

VEDERNIKOV, YU.P. & AFRIKANOV, I.I. (1969). On the role of a central adrenergic mechanism in morphine analgesic action. *J. Pharm. Pharmac.*, **21**, 845-847.

VOGT, M. (1954). The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *J. Physiol., Lond.*, **123**, 451-481.

WAND, P., KUSCHINSKY, K. & SONTAG, K.-H. (1973). Morphine-induced muscular rigidity in rats. *Eur. J. Pharmac.*, **24**, 189-193.

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