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IMIPRAMINE NORMALIZES NATURALLY-OCCURRING AND DRUG-INDUCED DIFFERENCES IN THE EXPLORATORY ACTIVITY OF RATS

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1 Exploratory activity of female hooded rats was measured in a Y maze on two occasions, 1 week apart. Locomotion (maze arm entries), rearing, and head-dipping into pots were scored for 5 min at each trial.

2 In control rats, differences between individuals in the amount of locomotion and rearing were consistent, as shown by significant test-retest correlations ($r = +0.55$, and $+0.83$ respectively). There was no correlation between head-dipping scores obtained in the two tests.

3 Imipramine (Imip) pretreatment before the second trial (10 mg/kg i.p. on the 3 preceding days, and 2.5 mg/kg 1 h before) abolished these correlations. The scatter of the scores about the mean was also reduced by Imip, but there was no significant change in mean scores. Thus Imip appeared to have a 'normalizing' effect on locomotion and rears: after pretreatment, scores tended to be more uniform, and no longer reflected naturally-occurring individual differences.

4 Imip abolished the changes in exploratory activity produced by drugs which alter brain 5-hydroxytryptamine metabolism: *p*-chlorophenylalanine (100 mg/kg 24 h before testing) increased and DL-5-hydroxytryptophan (12.5 mg/kg 1 h before testing) decreased the fall in activity over the trial in saline-treated rats but not that in Imip-treated rats. In this case, Imip also produced an overall reduction in activity scores.

5 The normalizing effects of Imip on rat behaviour may be analogous to its therapeutic effects in human depressive disorders.

Introduction

Differences in the amount of exploratory activity shown by individual rats in novel environments are consistent and stable over time (Irmiš, Radil-Weiss, Lát & Krekule, 1970), and are positively correlated with measures of brain 5-hydroxytryptamine (5-HT) turnover (Rosecrans, 1970), and inversely correlated with 5-HT concentration in the brain (Sudak & Mass, 1964). In a previous study (Harrison-Read & Steinberg, 1980), rats' exploratory activity scores were found to be more uniform after short-term pretreatment with the tricyclic antidepressant drug (TAD) imipramine (Imip), and no longer to reflect the naturally-occurring stable individual variation characteristic of control rats. This 'normalizing' effect of Imip on individual differences was characterized by the abolition of positive test-retest correlations for exploratory activity measured before and after pretreatment, and by the reduced scatter of individual scores about mean values which were not significantly affected by the drug.

The present study investigates the possibility that short-term pretreatment with Imip reduces both naturally-occurring differences in exploratory activity and those resulting from the actions of drugs which are known to have opposite effects on brain 5-HT synthesis. *p*-Chlorophenylalanine (PCPA) was given in a dose likely to cause partial inhibition of 5-HT synthesis (Koe & Weismann, 1966). 5-Hydroxytryptophan (5-HTP), the immediate metabolic precursor of 5-HT, was given in a small dose, within the range which causes a relatively specific increase in the 5-HT synthesis of 5-hydroxytryptaminergic neurones (Corrodi, Fuxe, & Hökfelt, 1967).

Methods

Female Lister hooded rats, aged approximately 4 months, were used in the experiments. The rats had not been used in any previous experiments, and they

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were kept under uniform conditions, approximately 16 to a large cage, for about two months before the start of the experiment. (Room temperature was maintained at 21 ± 2°C, artificial lighting was switched on at 06 h 00 min and off at 18 h 00 min, and masking noise was provided by an air conditioning unit). During this time the rats were not handled, and disturbance was kept to a minimum. Food and water were available *ad libitum* throughout.

Experiment 1

On day 1, 33 rats (mean weight ± s.d. = 188 ± 17 g) were tested individually in a maze by a standard procedure (Steinberg, Rushton & Tinson, 1961). The maze was a symmetrical Y-shaped runway, with walls 33 cm high, and an open top. Each arm was 38 cm long and 13 cm wide, and contained an empty earthenware pot at the far end. Rats were tested in random order, between 11 h 45 min and 16 h 00 min. A trial consisted of taking a rat from its cage, placing it in the centre of the maze, and observing it for 5 min. The number of entries with all four feet into any of the arms of the maze (locomotion), the number of rears onto the hind legs, and the number of times the rat dipped its snout into the pots, were recorded over successive 30 s intervals throughout the trial. At the end of the trial, the rat was gently removed from the maze, weighed and marked with dye for identification, and then replaced in its home cage. The maze was wiped clean before another rat was tested.

Rats were subsequently divided into two groups of 16 and 17 rats. Allocation was made on a quasi-random basis so that the rats in each group were approximately matched for exploratory activity scores. On days 2, 3, and 4 all rats were injected intraperitoneally with saline (0.15 M NaCl, 2 ml/kg), and then on days 5, 6, and 7, one group was given imipramine hydrochloride (Imip, 10 mg/kg). The drug was dissolved in saline, and fresh solutions were made up each day. This pretreatment schedule ensured that all rats received the same number of injections and a comparable amount of handling as the rats in a previous study (Harrison-Read & Steinberg, 1980).

On day 8, the dose of Imip was reduced to 2.5 mg/kg in order to avoid sedative effects, and all rats were retested in the Y maze, 1 h after injection, as described above. The order in which rats were tested on this second trial was re-randomized, and as on day 1, rats were tested between 11 h 45 min and 16 h 00 min.

Experiment 2

Female hooded rats (n = 104) with a mean ± s.d. weight of 191 ± 22 g were allocated at random to 2 groups of 52 rats each. On the morning of day 1, rats were weighed and marked with dye for identification. Rats from one group were injected intraperitoneally with saline (2 ml/kg), and those in the other group were given an equivalent volume of a solution of imipramine hydrochloride in saline (Imip, 10 mg/kg). The injections were repeated on days 2 and 3, using fresh solutions each day. On day 3, approximately one third of the rats in both groups were also given an injection of *p*-chlorophenylalanine (PCPA, 100 mg/kg i.p.). The drug was suspended in a 1% (v/v) solution of Tween-80 made up in saline, and injected in a volume of 2 ml/kg. The remainder of the saline- and Imip-treated rats received an equivalent volume of the vehicle solution alone. On day 4, approximately half of these rats were given DL-5-hydroxytryptophan (5-HTP, 12.5 mg/kg i.p.), suspended and dissolved in the Tween-80 vehicle used previously, and injected in a volume of 2 ml/kg. All of the other rats were injected with an equivalent volume of the vehicle alone. In addition, all rats were injected with saline or Imip as appropriate, but on this occasion, the dose of Imip was reduced to 2.5 mg/kg. This pretreatment schedule resulted in 6 groups: saline-vehicle (n = 18), saline-PCPA (n = 17), saline-5-HTP (n = 17), Imip-vehicle (n = 18), Imip-PCPA (n = 16), and Imip-5-HTP (n = 18).

All rats were tested for the first time in the Y maze, in random order, 1 h after the last injections on day 4. The method of testing was the same as described for experiment 1 except that the earthenware pots were omitted.

Results

Effect of imipramine on naturally-occurring individual differences in activity

In control rats, individual differences in locomotion (entries) and rearing in the Y maze were stable over a 1 week period as shown by the significant test-retest correlations for the scores obtained before and after treatment (Figure 1, Table 1). Individual differences in head-dips into the pots did not show a significant test-retest correlation (Table 1). Entries and rears were positively correlated before treatment (r = +0.74, d.f. = 31, $P < 0.001$), but neither of these measures correlated with the number of head-dips (for entries, r = −0.21, for rears, r = −0.09).

Imip pretreatment completely abolished test-retest correlations for entries and rears (Figure 1, Table 1), the coefficients obtained being significantly different from the corresponding control values, Z = 2.24,

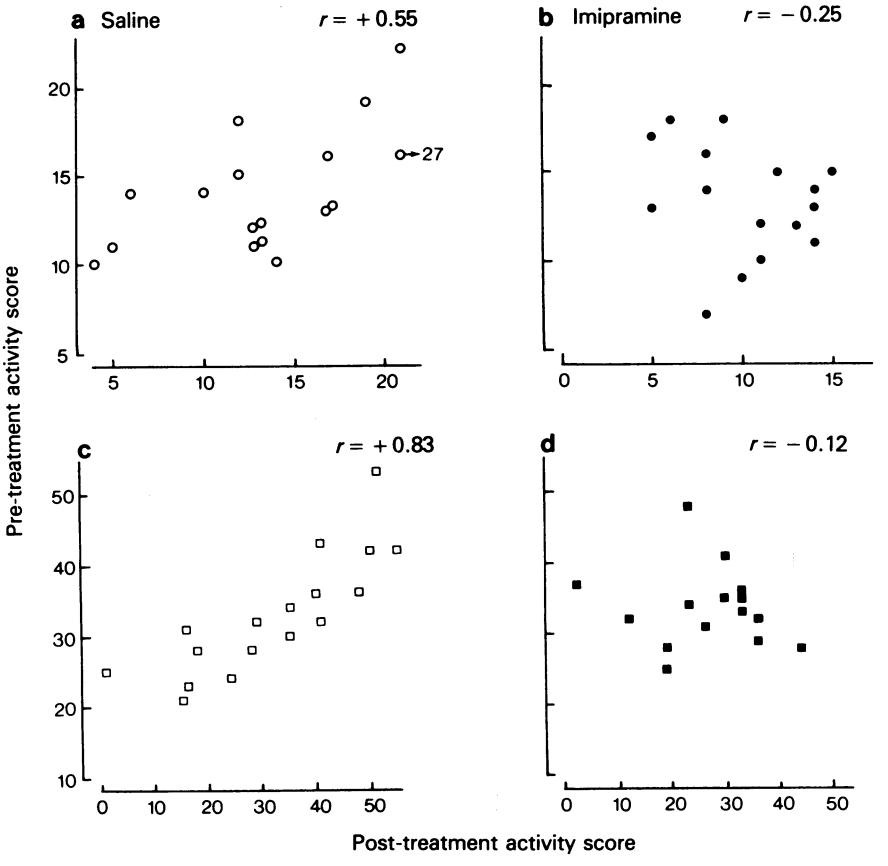

Figure 1 Y maze activity scores of individual rats (5 min totals) obtained before and after pretreatment with saline (a and c; entries ○, rears □) or imipramine (b and d; entries ●, rears ■). Imipramine pretreatment abolished the significant test-retest correlations which were found in control rats, although the mean activity scores of the two groups were not significantly different.

Table 1 Effect of sub-acute pretreatment with imipramine on exploratory activity of rats in a Y maze

	Trial	*Entries*	*Rears*	*Head-dips*
Saline	1	13.9 ± 0.8	32.9 ± 2.0	4.5 ± 0.5
$n = 17$	2	13.6 ± 1.5	32.1 ± 3,7	4.2 ± 0.7
		$r = +0.55$*	$r = +0.83$***	$r = -0.13$
Imipramine	1	13.4 ± 0.8	32.2 ± 1.9	4.6 ± 0.7
$n = 16$	2	10.2 ± 0.8	26.7 ± 2.6	2.5 ± 0.6
		$r = -0.25$†	$r = -0.12$‡	$r = +0.44$

Exploratory activity scores (means ± s.e. mean) obtained during 5 min trials before (1) and after (2) treatment with saline or imipramine (n = number of subjects per group). Effects on individual differences in exploratory activity were assessed by calculating product-moment correlation coefficients (r) for scores obtained at trials 1 and 2. Significance of difference of correlation coefficients from zero: *$P < 0.05$, ***$P < 0.001$; significance of difference from coefficient of saline control group: †$P < 0.05$, ‡$P < 0.01$.

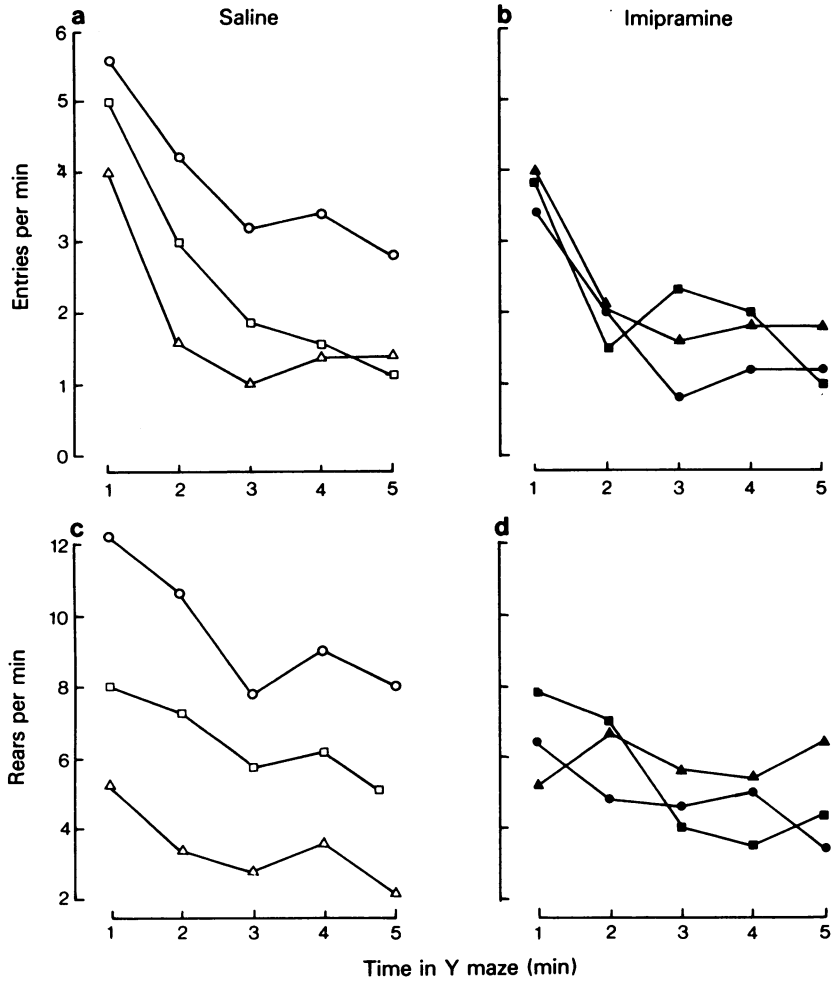

Figure 2 Mean Y maze activity scores for each minute of the trial (arm entries, a and b; rears, c and d) in saline and imipramine pretreated rats ranked into 3 groups on the basis of activity scores obtained 1 week previously, before treatment was begun. The differences between scores of control rats with previously high (○, $n = 5$), intermediate (□, $n = 7$), and low (△, $n = 5$) total activity scores were still present after saline pretreatment (for entries, $F = 5.39$, $P < 0.02$; for rears, $F = 11.89$, $P < 0.001$, d.f. = 2,14 in both cases), whereas after imipramine pretreatment, the differences between rats with previously high (●, $n = 5$); intermediate (■, $n = 6$) and low (▲, $n = 5$) total activity scores were abolished (for entries, $F = 0.84$; for rears, $F = 0.27$, d.f. = 2,13 in both cases). There were significant interactions between the scores of rats grouped according to their previous activity, and imipramine pretreatment (for entries, $F = 5.81$; for rears $F = 7.40$, d.f. = 2,27, $P < 0.01$ in both cases).

$P < 0.02$; and $Z = 3.39$, $P < 0.01$ respectively;

$$Z = \frac{|z_1 - z_2|}{\sqrt{1/(n_1 - 3) + 1/(n_2 - 3)}}$$

(Snedecor & Cochran, 1967).

The scatter of individual scores was also reduced by Imip (Table 1), but only in the case of entries was the variance ratio for scores obtained in control and Imip rats significant (for entries, $F = 3.30$, $P < 0.05$, for rears, $F = 2.26$, $P < 0.1$, d.f. = 14, 15 in both cases). Although Imip pretreatment tended to reduce mean activity scores slightly, none of the differences

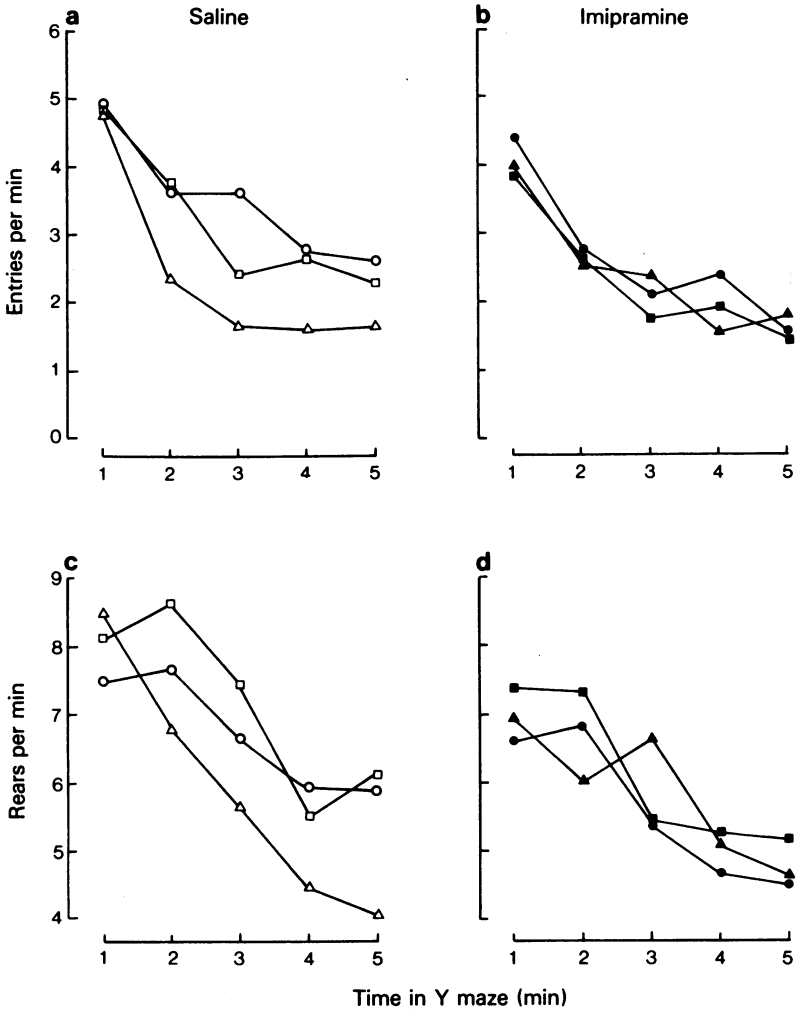

Figure 3 Mean Y maze activity scores for each minute of the trial (arm entries, a and b; rears, c and d) in saline and imipramine pretreated rats, treated in addition with *p*-chlorophenylalanine (PCPA), 5-hydroxytryptophan (5-HTP), or the vehicle solution as a control. The activity curves of saline PCPA rats (△,n = 17) fell more steeply over the trial than did those of saline-vehicle rats (□, n = 18), whereas activity curves of saline 5-HTP rats (○, n = 17) tended to fall less steeply. When pretreated with imipramine, activity curves of PCPA (▲, n = 18), 5-HTP (●, n = 16) and control (■, n = 18) rats appeared similar.

between the scores of control and Imip rats at trial 2 were statistically significant (two-tailed *t*-tests).

The 'normalizing' effect of Imip on individual differences in locomotion and rearing was also demonstrated by the activity curves of rats ranked into high, intermediate, and low categories with respect to their activity scores obtained before treatment (Figure 2). The curves of activity against time in the maze of control rats ranked in this way were clearly separated after treatment, whereas those of Imip rats virtually overlapped.

Effect of p-*chlorophenylalanine and* 5-*hydroxytryptophan on the exploratory activity of saline pretreated rats*

In saline pretreated rats, there were differences among the vehicle-control, PCPA, and 5-HTP groups in the

fall in exploratory activity over the 5 min trial (Figure 3). The differences were seen most clearly in the case of locomotion (entries), since initial activity levels were nearly the same for all 3 pretreatment groups: PCPA increased the fall in activity whereas 5-HTP tended to reduce it. In an analysis of variance of the entries scores, with repeated measures for each minute of the trial, there was a significant main effect of PCPA and 5-HTP treatment ($F = 4.95$, d.f. = 2,49, $P < 0.02$) and a significant interaction between drug treatments and minutes of the trial ($F = 2.58$, d.f. = 8,196, $P < 0.02$). The main effect and interaction in the case of rears just failed to reach significance ($F = 2.79$, d.f. = 2,49, and $F = 1.82$, d.f. = 8,196, $P < 0.1$ in both cases).

When entries scores of PCPA- and 5-HTP-treated rats were compared separately with controls, the interactions between drug treatment and minutes of the trial just failed to reach significance in each case (for PCPA, $F = 2.28$, for 5-HTP, $F = 2.35$, d.f. = 4,132, $P < 0.1$ in both cases), although there was a significant main effect of PCPA ($F = 6.26$, d.f. = 1,33, $P < 0.02$). However, when the entries scores of PCPA- and 5-HTP-treated rats were compared with each other, both the main effect, and the interaction with minutes of the trial were significant ($F = 8.29$, d.f. = 1,32, $P < 0.01$, and $F = 3.02$, d.f. = 4,128, $P < 0.02$ respectively). In other words, there was a significant difference between PCPA- and 5-HTP-treated rats in the extent to which locomotion decreased during the trial.

Effects of p-chlorophenylalanine and 5-hydroxytryptophan in imipramine pretreated rats

In rats pretreated with Imip, additional treatment with PCPA and 5-HTP had no apparent effect on exploratory activity (Figure 3), (for entries, $F = 0.80$, for rears, $F = 0.34$, d.f. = 2,49, $P > 0.1$ in both cases). The action of Imip was compared with that of control treatment by two-way analyses of variance with repeated measures for minutes of the trial. Significant main effects of Imip (for entries, $F = 9.60$, d.f. = 1,98 $P < 0.01$, for rears $F = 4.45$, d.f. = 1,98, $P < 0.05$) indicated that Imip reduced overall activity levels. The abolition by Imip of activity differences due to PCPA and 5-HTP was reflected by the significant interaction in the case of entries between sub-acute (saline or Imip) and acute pretreatment (PCPA, 5-HTP, or vehicle) and minutes of the trial ($F = 2.30$, d.f. = 8,392, $P < 0.05$). Although this interaction was not significant for rears ($F = 1.46$, d.f. = 8,392, $P < 0.2$), when the generalised depressant effect of Imip was removed by expressing results as changes from the mean activity scored in the first minute of the trial, there were significant interactions between the effects of acute and sub-acute drug treatments for both entries and rears ($F = 4.49$ and $F = 3.11$ respectively, d.f. = 2,98, $P < 0.05$ in both cases).

Change in body weight in drug pretreated rats

The mean body weight ($\pm$s.e. mean) of Imip pretreated rats fell by 10.0 ± 1.1 g ($n = 16$) in experiment 1, and by 7.4 ± 2.1 g ($n = 36$) in experiment 2 over the 3 days of pretreatment. Controls gained 1.1 ± 1.1 g ($n = 17$) and 0.7 ± 0.7 g ($n = 35$) over the same period, the differences between Imip-treated and control rats being highly significant in both cases ($P < 0.01$, two-tailed t-tests). The weight lost by control and Imip rats over the 24 h after receiving PCPA (1.3 ± 0.7 g and 2.9 ± 1.4 g respectively) was not significantly different.

Discussion

The finding that individual differences in certain aspects of rats' exploratory behaviour in a Y maze are normally stable over time confirms previous work (Harrison-Read, 1978; 1979; Harrison-Read & Steinberg, 1980). The possibility that significant test-retest correlations for exploratory activity in control rats resulted from reproducible effects of testing order, or time of day, was excluded by randomizing order and time of day of testing on both occasions. It is conceivable that individual differences in body weight may also contribute to individual differences in motor activity, but this possibility was discounted in the earlier study (Harrison-Read & Steinberg, 1980). Because female rats were used in these experiments, another possibility is that differences in the state of oestrus were partly responsible for the individual differences in exploratory activity. This cannot be excluded here, but it seems unlikely because consistent individual differences in exploratory activity are also found in male rats, and these cover a comparable range of values to those in females (Harrison-Read, 1978).

The most likely explanation for the consistency of individual differences in exploratory activity is that they depend on inherent properties of the brain (Harrison-Read, 1978; 1979).

Imip pretreatment appeared to abolish these hypothetical properties of the brain, or to prevent them from finding expression in behaviour, because the variability of locomotion and rearing scores after pretreatment no longer reflected the consistent individual differences seen in control rats. Also Imip pretreatment reduced the scatter of the scores without significantly altering their mean value, although Imip did reduce activity scores slightly in experiment 1, and in experiment 2 this effect was statistically significant. Thus, Imip pretreatment abolished naturally-occurring individual differences in response to a novel

environment, and made rats more uniform in their behaviour, at least as reflected by locomotion and rearing.

As found in the earlier study (Harrison-Read & Steinberg, 1980), the normalizing effect of Imip was confined to individual differences in locomotion and rearing in the Y maze. The test-retest correlation for head-dipping into pots, possibly a more specific index of exploratory behaviour (Robbins, 1977), was if anything increased by the drug. This suggests that the normalizing effect of Imip on entries and rears was unlikely to be due to non-specific disruption of behaviour or to state-dependent dissociation of cognitive functions. Presumably Imip affected motor rather than perceptual processes involved in exploratory behaviour.

It is also possible that the normalizing effect of Imip on exploratory activity was somehow related to the weight loss it produced. Although this cannot be ruled-out it seems unlikely in view of our finding that a single dose of protriptyline and repeated doses of Imip had similar effects on individual differences in activity (Harrison-Read & Steinberg, 1980), since in the former case there was insufficient time for weight loss to occur.

The tendency for drugs with opposite effects on 5-HT synthesis (PCPA and 5-HTP) to produce opposite changes in exploratory activity suggests that individual differences in the function of 5-HT in the brain may be the cause of the individual variability in behaviour, particularly as the changes in brain 5-HT concentration resulting from the doses of PCPA and 5-HTP used here (typically in the order of $\pm 40\%$, Koe & Weissman, 1966; Moir & Eccleston, 1968) are probably comparable to the extreme values arising from normal variation. However, the functional significance of drug-induced and naturally-occurring differences in brain 5-HT concentration may not be the same, and in any case, some of the behavioural actions of PCPA and 5-HTP may be due to peripheral rather than central alterations in 5-HT synthesis. Furthermore, both PCPA and 5-HTP have effects in addition to their principal actions on 5-HT systems, e.g. PCPA also slightly depletes the brain of noradrenaline (NA) (Koe & Weissman, 1966), and 5-HTP may be taken up into catecholaminergic neurones and converted to 5-HT which can cause release of NA and dopamine, or exert effects at sites where it is not normally present (Fuxe, Butcher & Engel, 1971). However, when 5-HTP is given in low doses (20 mg/kg or less) as here, the synthesis and release of 5-HT is increased only in 5-hydroxytryptaminergic pathways (Corrodi & Fuxe, 1968; Trulson & Jacobs, 1976).

In previous experiments (Harrison-Read & Steinberg, 1980), a single dose of protriptyline, a secondary amine TAD which is a very potent blocker of the neuronal reuptake of NA (Carlsson, Corrodi, Fuxe & Hökfelt, 1969b), also had a normalizing effect on individual differences in exploratory activity. By contrast, single and repeated doses of chlorimipramine, a tertiary amine TAD with a predominant effect on the re-uptake of 5-HT (Carlsson, Corrodi, Fuxe & Hökfelt, 1969a) either had no effect, or increased test-retest correlations for exploratory activity. From these findings it was concluded that normalization of individual differences may result directly or indirectly from TAD-induced blockade of neuronal reuptake of NA. A predominant effect on the reuptake of NA after short-term pretreatment with Imip is likely because when equilibrium is reached after 3 to 4 days of once daily injections, the concentration in the brain of the secondary amine metabolite desipramine is at least twice that of the parent drug (Nagy, 1977). Desipramine, like protriptyline, is a potent and specific blocker of the neuronal reuptake of NA (Carlsson *et al.*, 1969b).

The present results suggest that, by blocking the reuptake of NA at nerve endings, Imip may alter activity in noradrenergic pathways and thereby reduce the behavioural expression of inherent differences in brain 5-HT activity. As a consequence, rats' behaviour may be determined to a greater extent by environmental influences, which, if the same for all individuals, will lead to a certain uniformity in the exploratory activity of a group of rats. Although perhaps highly speculative, it should be possible to test this hypothesis experimentally.

In the same way, an effect on noradrenergic neurotransmission may also account for the abolition by Imip of the behavioural effects of both PCPA and 5-HTP. However, more direct effects on 5-HT mechanisms must also be considered. For example, blockade of neuronal reuptake of 5-HT by Imip (Carlsson *et al.*, 1969a), and increased sensitivity to the effects of 5-HT, which develops in neurones receiving a 5-hydroxytryptaminergic input after 4 to 7 days pretreatment with Imip (de Montigny & Aghajanian, 1978), might both compensate for the reduced 5-HT release presumed to result from inhibition of 5-HT synthesis by PCPA. On the other hand, Imip reduces turnover of 5-HT (Corrodi & Fuxe, 1968; Schubert, Nybäck & Sedvall, 1970), probably by inhibiting electrical activity in 5-hydroxytryptaminergic neurones (Sheard, Zolovick & Aghajanian, 1972). This might be expected to slow production of 5-HT from 5-HTP, and thereby to reduce the latter's effect on behaviour. An investigation of the effects of drugs such as chlorimipramine and protriptyline should be useful for deciding whether the abolition by Imip of PCPA- and 5-HTP-induced behaviours depends mainly on 5-hydroxytryptaminergic or noradrenergic mechanisms.

There is a striking parallel between the normalizing effect of Imip on exploratory activity in rats and the

therapeutic action of the drug in human depressive disorders. Imip, and TADs in general, appear to normalize many of the seemingly diverse manifestations of depression, with apparently minimal specific effects in normal people (Klein, 1970; Mendels & Frazer, 1975). The failure, mentioned above, to find a normalizing effect with chlorimipramine on rat behaviour can be reconciled with the established antidepressant effect of this drug, because in rats, the concentration in the brain of chlorimipramine is five times greater than that of its secondary amine metabolite (Nagy, 1977), whereas in humans, plasma concentration of chlorimipramine after oral administration is only half that of the metabolite (Nagy & Johansson, 1977). An excess concentration in the brain of the metabolite of chlorimipramine should produce a predominant effect on the reuptake of NA in man.

By analogy with the hypothesis outlined above, the therapeutic effects of TADs may depend on compensatory changes in noradrenergic pathways which mitigate the effects of abnormally high or abnormally low activity in 5-HT systems in the brain. This helps to reconcile the evidence which suggests a role for 5-HT in the aetiology of depression (Murphy, Campbell, & Costa, 1978) with a view that the predominant pharmacological action of TADs is on noradrenergic mechanisms (Ross & Renyi, 1975; Shaw, Riley, Michalakeas, Tidmarsh & Blazek, 1977). Our results also suggest that greater attention should be paid to individual differences in considering the effects of TADs in normal people. However, further speculation on the relevance of these behavioural actions of Imip in rats to its antidepressant action in man must await further experiments. In particular, the effect of more prolonged pretreatment must be studied, since administration for days or weeks is necessary both for an antidepressant effect in man and for changes in monoamine receptor sensitivity to occur in experimental animals (Sulser, Vetulani & Mobley, 1977; de Montigny & Aghajanian, 1978).

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