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DECREASES IN TYROSINE AND *p*-HYDROXYPHENYLGLYCOL CAUSED BY VARIOUS ANTIDEPRESSANTS

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Abstract—The effects of eleven different antidepressant drugs on brain *p*-hydroxyphenylglycol (pHPG) and on brain and plasma tyrosine concentrations were investigated in rats. Imipramine, amitriptyline, amoxapine, desmethylimipramine and iprindole (20 mg/kg each) and bupropion (50 mg/kg) decreased brain pHPG levels 4.5 or 6 hr after injection. Each of these drugs also significantly reduced plasma tyrosine levels 1.5 hr after injection. In contrast, zimelidine, amitriptylinoxide, trimipramine and trazodone had no significant effect on either brain pHPG or plasma tyrosine. Mianserin significantly lowered plasma tyrosine but produced a nonsignificant decrease in brain pHPG. The decreases in brain pHPG caused by the various drugs were significantly correlated with 3,4-dihydroxyphenylethyleneglycol. Moreover, decreases in brain pHPG and brain and plasma tyrosine concentrations were correlated with the potencies of these drugs to inhibit *in vitro* norepinephrine uptake. These results suggest the possibility that noradrenergic (or similar) mechanisms regulate both pHPG and tyrosine levels. However, the decreases in pHPG cannot be explained entirely by a deficiency in tyrosine, since the depletions in pHPG were much larger and longer lasting than those of tyrosine.

Recent studies in our laboratory demonstrated that the antidepressant drugs, imipramine and iprindole, cause substantial decreases in both brain and urine concentrations of the octopamine metabolite, *p*-hydroxyphenylglycol (pHPG) [1]. Subsequent results indicated that the effects of imipramine on pHPG are probably due partly to a lowering of brain and plasma tyrosine levels and partly to inhibition of the conversion of tyrosine to pHPG [2]. We have now investigated various other antidepressants, including several atypical ones, for their effects on brain and plasma tyrosine, on brain pHPG and on brain catecholamines and their metabolites in order to (1) better understand the relationships among the levels of these compounds and (2) determine whether the depletion in either tyrosine or pHPG is a general feature of all antidepressants and may, therefore, have a possible role in their therapeutic actions.

MATERIALS AND METHODS

Male Sprague–Dawley rats (200–250 g) were housed individually with a 12-hr light–dark cycle and with free access to food and water for 1 week before being injected intraperitoneally (i.p.) with isotonic saline (5 ml/kg) or one of the drugs studied, dissolved in saline just before injection and given in a dose equivalent to 20 mg/kg (50 mg/kg for bupropion) of the free base. Animals were killed by decapitation 1.5, 4.5 or 6 hr following treatment (24 hr in those experiments where urine was collected). Trunk blood was collected into a plastic beaker containing 200 μl of heparin. Brains were rapidly removed, blotted and dissected longitudinally on an ice-cold glass plate. The blood samples were kept on ice for up to 1.5 hr and centrifuged at 500 *g* for 15 min. Plasma was stored at 4° until assayed (within 1 week). The brain halves were immediately frozen on dry ice and stored at −50°. One brain half was used for the simultaneous assay of pHPG, 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) and 3,4-dihydroxyphenylethyleneglycol (DHPG) by gas chromatography–mass spectrometry (GC–MS) with chemical ionization as previously described [2]. Urinary pHPG levels were measured by a similar procedure [1]. The remaining brain half was used for determining the concentrations of tyrosine [3] and of norepinephrine (NE), dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC), by HPLC with electrochemical detection [4]. Plasma tyrosine was also assayed by HPLC with electrochemical detection [3].

Authentic pHPG was provided by Dr. J. Stephen Kennedy, Neurosciences Research Branch, NIMH. The following drugs were donated: imipramine HCl (CIBA-Geigy, Summit, NJ); desmethylimipramine HCl (USV Pharmaceuticals, Tuckahoe, NY); amitriptyline HCl (Merck Sharp & Dohme, West Point, PA); bupropion HCl (Burroughs Wellcome, Research Triangle Park, NC); zimelidine di-HCl (Astra, Sodertalje, Sweden); mianserin HCl (Organon, Oss, The Netherlands); trazodone HCl (Bristol-Meyers, Evansville, IN); amoxapine HCl (Lederle, Pearl River, NY); trimipramine maleate and iprindole HCl (Wyeth, Philadelphia, PA); amitriptylinoxide dihydrate (A. Nattermann, Cologne,

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Table 1. Effects of various antidepressant drugs on plasma tyrosine and on pHPG, tyrosine, and catecholamines and their metabolites in whole rat brain

Drug	hr	Brain pHPG	Brain tyrosine	Plasma tyrosine	Brain MHPG (% of control)	Brain DHPG	Brain NE	Brain DA	Brain DOPAC
Imipramine	4.5	52 ± 10*	89 ± 4	74 ± 4	88 ± 4†	67 ± 7‡	96 ± 2	90 ± 4	94 ± 7
	1.5	§	84 ± 6†	79 ± 7‖	§	§	§	§	§
Amitriptyline	4.5	55 ± 13¶	77 ± 8†	68 ± 5†	115 ± 2¶	86 ± 3	102 ± 4	97 ± 3	100 ± 5
	1.5	§	80 ± 6‖	69 ± 4‡	§	§	§	§	§
Amoxapine	4.5	56 ± 9**	100 ± 5	102 ± 22	86 ± 13	71 ± 10¶	105 ± 5	93 ± 3	248 ± 21**
	1.5	§	69 ± 7†	65 ± 2**	§	§	§	§	§
Desmethylimipramine	4.5	67 ± 6†	94 ± 4	74 ± 4**	63 ± 5†	60 ± 10†	89 ± 2‡	86 ± 4	88 ± 7
	1.5	§	83 ± 7	73 ± 4‡	§	§	§	§	§
Iprindole	6	69 ± 7‡	§	§	§	§	101 ± 4	94 ± 5	100 ± 10
	1.5	§	89 ± 4	84 ± 4†	§	§	§	§	§
Bupropion	6	74 ± 11†	§	§	§	§	93 ± 3	92 ± 5	99 ± 4
	1.5	§	95 ± 8	68 ± 5‡	§	§	§	§	§
Zimelidine	4.5	76 ± 9	115 ± 6	71 ± 4	85 ± 5†	72 ± 4¶	§	§	§
	1.5	§	88 ± 6	90 ± 3	§	§	§	§	§
Mianserin	4.5	77 ± 15	119 ± 10	103 ± 14	132 ± 11†	90 ± 9	97 ± 5	85 ± 6	98 ± 6
	1.5	§	86 ± 7	68 ± 4‡	§	§	§	§	§
Amitriptylinoxide	4.5	89 ± 8	99 ± 8	103 ± 6	74 ± 3	100 ± 4	107 ± 4	97 ± 4	95 ± 4
	1.5	§	102 ± 4	94 ± 3	§	§	§	§	§
Trimipramine	4.5	114 ± 7	89 ± 4	91 ± 8	91 ± 6	104 ± 9	102 ± 1	105 ± 3	132 ± 11
	1.5	§	84 ± 4*	87 ± 6	§	§	§	§	§
Trazodone	4.5	125 ± 25	110 ± 11	86 ± 3	111 ± 4	103 ± 7	§	§	§
	1.5	§	91 ± 8	90 ± 4	§	§	§	§	§

All drugs were given at a dose of 20 mg/kg, i.p., except for bupropion (50 mg/kg, i.p.). The values are compiled from seven experiments and each represents the mean ± SE of the percentage of a control group from that experiment. The averages of the means of the saline-treated groups were: brain pHPG, 3.20 ng/g; brain tyrosine, 13.5 μg/g; plasma tyrosine, 18.9 μg/ml; brain MHPG, 103 ng/g; brain DHPG, 132 ng/g; brain NE, 356 ng/g; brain DA, 775 ng/g; and brain DOPAC, 113 ng/g. Each drug-treated group was statistically compared to the corresponding controls with a two-tailed Student's *t*-test.

* $P < 0.01$.
† $P < 0.05$.
‡ $P < 0.005$.
§ Samples were not assayed.
‖ $P < 0.025$.
¶ $P < 0.02$.
** $P < 0.001$.

West Germany) and chlorpromazine HCl (Smith Kline & French, Philadelphia, PA).

RESULTS

Table 1 shows the acute effects of a single dose of eleven antidepressant drugs on brain pHPG, on brain and plasma tyrosine concentrations, and on brain catecholamines (NE and DA) and their metabolites (MHPG, DHPG and DOPAC). Significant decreases in brain pHPG levels were found for imipramine, amitriptyline, amoxapine, desmethylimipramine and iprindole (20 mg/kg each) and for bupropion (50 mg/kg) either 4.5 or 6 hr after administration. Small but nonsignificant decreases were seen after 20 mg/kg of zimelidine ($P < 0.1$), mianserin and amitriptylinoxide, whereas trimipramine and trazodone had no apparent effect. Brain pHPG levels were not measured in the animals killed 1.5 hr after injection, since our previous studies with imipramine have indicated that it causes a decline in pHPG that is delayed 3 to 4.5 hr [1, 2].

The same six antidepressants that significantly reduced brain pHPG at 4.5 or 6 hr also significantly lowered plasma tyrosine at 1.5 hr. Moreover, the five antidepressants that had no significant effect on brain pHPG at 4.5 hr also failed to lower plasma tyrosine significantly at 1.5 hr, except for mianserin (to 68% of control). Plasma tyrosine levels (at 1.5 hr) and brain pHPG (at 4.5 to 6 hr) for all the antidepressants were statistically correlated (Pearson correlation, $r = 0.675$, $P < 0.05$). However, brain tyrosine levels (at 1.5 hr) were not statistically correlated with brain pHPG at 4.5 hr ($r = 0.511$, NS), presumably due to the smaller effect in brain.

Plasma tyrosine was decreased significantly 4.5 hr only after injection of amitriptyline and desmethylimipramine. (Iprindole and bupropion were not studied at 4.5 hr.)

The reductions in brain tyrosine were generally smaller than for plasma. Desmethylimipramine, mianserin, iprindole and bupropion, all of which decreased plasma tyrosine, failed to lower brain tyrosine levels significantly. Only one drug, trimipramine, significantly lowered brain tyrosine without significantly reducing plasma tyrosine.

Three of the antidepressants, imipramine, desmethylimipramine and zimelidine, reduced brain MHPG levels; they, in addition to amoxapine, also lowered brain DHPG. However, two drugs, amitriptyline and mianserin, significantly elevated brain MHPG but had no influence on DHPG. Surprisingly, the concentration of pHPG in brain 4.5 hr after the administration of various antidepressant drugs, although not significantly correlated with MHPG concentrations ($r = 0.143$; Fig. 1A), was significantly correlated with DHPG (Pearson correlation, $r = 0.791$, $p < 0.02$; Fig. 1B). However, brain DHPG was not correlated significantly with plasma or brain tyrosine or with brain MHPG. DOPAC levels were unchanged, except for a large increase (to 248% of control) produced by amoxapine and a nearly significant increase (to 132%, $p < 0.1$) due to trimipramine. These data are in accordance with previous reports that amoxapine [5] and trimipramine

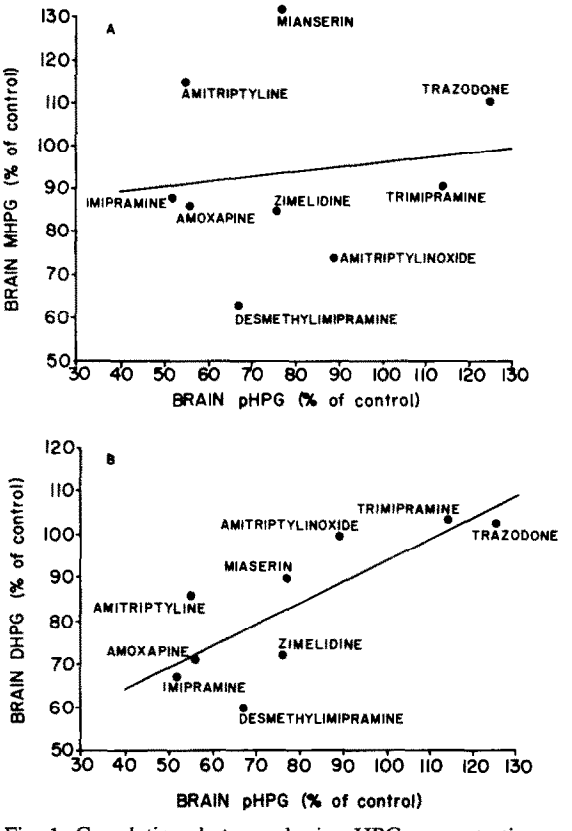

Fig. 1. Correlations between brain pHPG concentrations after treatment with various antidepressants with: (A) brain MHPG ($r = 0.143$; slope = 0.118; not significant); and (B) brain DHPG ($r = 0.791$; slope = 0.507, $P < 0.02$). MHPG, DHPG and pHPG were measured in the same tissue samples obtained from rats treated with a dose of 20 mg/kg, i.p. 4.5 hr before being killed. The data, expressed as a percentage of control, are from Table 1.

[6] exert potent and weak neuroleptic-like activities respectively.

Comparisons were made between the effects of these antidepressants on tyrosine and pHPG levels with their known potencies *in vitro* for blocking various amine uptake systems and neurotransmitter receptors in rat brain tissue. There were no significant correlations between brain pHPG or brain or plasma tyrosine levels and either serotonin or dopamine uptake [7], α_1, α_2, β_1 or β_2 adrenergic, muscarinic acetylcholine, histamine (H_1 and H_2), DA D-2 and serotonin receptors [8, 9]. However, there were significant correlations between plasma tyrosine (1.5 hr) ($r = -0.838$; $P < 0.01$), brain tyrosine ($r = -0.681$; $P < 0.05$) (Fig. 2) and brain pHPG (4.5 hr) ($r = -0.706$; $P < 0.05$) (Fig. 3) with the logarithm of the inhibitor constant, K_i, for blocking [^{3}H]NE uptake [7]. Brain DHPG ($r = -0.657$; $P < 0.1$) but not MHPG ($r = -0.021$) was correlated almost significantly with the K_i for NE uptake.

We next compared the ability of single doses of various antidepressants to alter pHPG and tyrosine levels acutely with the ability of repeated treatments with the same drugs to diminish the responsiveness of the NE-stimulated adenylate cyclase system [10]. The comparisons were made based on the results of

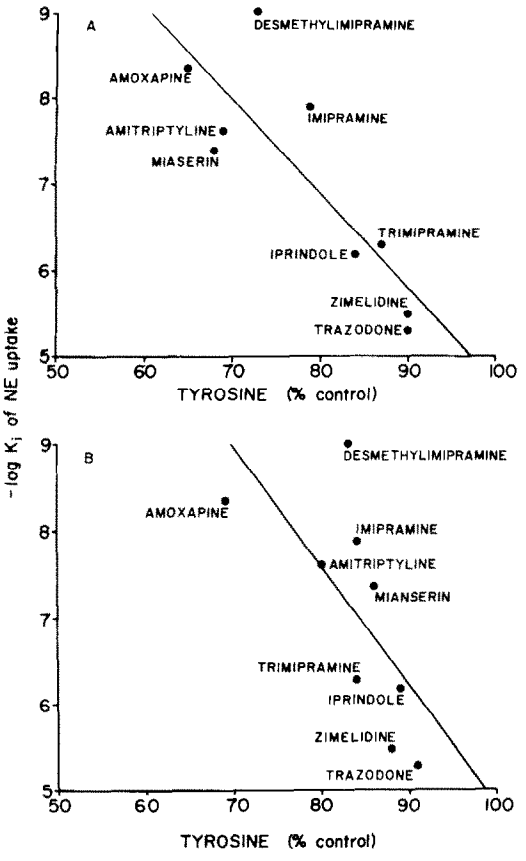

Fig. 2. Correlations between −log of published values of K_i, the inhibition constant for various antidepressants on [^{3}H]NE uptake into rat brain synaptosomes [7], with: (A) plasma tyrosine ($r = -0.838$, $P < 0.01$) and (B) brain tyrosine ($r = -0.681$, $P < 0.05$) concentrations. When amoxapine was excluded from the data in panel B, $r = -0.9608$ ($P < 0.001$). The antidepressant drugs (20 mg/kg, i.p.) were administered 1.5 hr before the animals were killed.

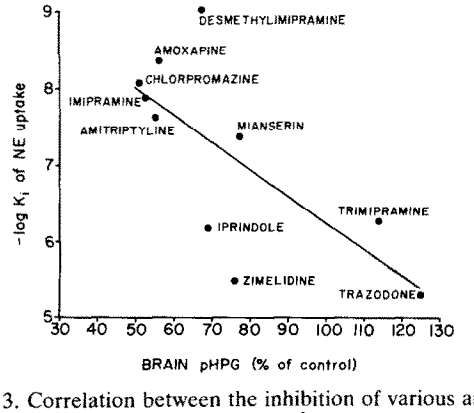

Fig. 3. Correlation between the inhibition of various antidepressants and chlorpromazine on [^{3}H]NE uptake into rat brain synaptosomes [7] with decreases in brain pHPG ($r = -0.706$; $P < 0.05$). All drugs were administered in a dose of 20 mg/kg, i.p., 4.5 hr before the animals were killed. The data for pHPG are taken from Table 1.

Kopanski *et al.* [11], since these authors investigated in one experiment five of the same antidepressants included in our studies. In their studies of the adenylate cyclase system, the antidepressants were administered in a dose of 30 mg/kg once daily for 9 days, as compared to a single injection of 20 mg/kg used in our studies. Although this comparison represents a small number of drugs and does not take into account differences in metabolism and distribution among the drugs *in vivo*, it is noteworthy that the four drugs (i.e. imipramine, amitriptyline, amoxapine and desmethylimipramine) that desensitized the adenylate cyclase system also significantly lowered brain pHPG. Trimipramine was ineffective in both systems. The correlation between desensitization of the adenylate cyclase system and decreases in pHPG was statistically highly significant ($r = 0.986$; $P < 0.01$), despite the small N. The decreases in NE-stimulated adenylate cyclase tended to be correlated with plasma tyrosine ($r = 0.845$; $P < 0.1$) and brain tyrosine ($r = 0.495$), but these correlations did not reach statistical significance, presumably due to the small number of drugs compared.

Since chlorpromazine, although not generally considered as an antidepressant, is structurally similar to imipramine and also inhibits NE uptake [7] and decreases the responsiveness of the NE-stimulated adenylate cyclase system [12], we decided to find out whether chlorpromazine also lowered brain pHPG. An experiment carried out as for the other drugs showed that chlorpromazine (20 mg/kg, 4.5 hr) decreased brain pHPG to 51% of control (to 1.76 ± 0.31 ng/g vs 3.46 ± 0.59 ng/g for saline controls; $P < 0.005$). These data, which are included in Fig. 3, indicate that the correlation between the pK_i for NE uptake and brain pHPG appears to hold for chlorpromazine as for the antidepressants.

Five antidepressants and chlorpromazine were examined for their effects on 24-hr urinary pHPG excretion (Table 2). Chlorpromazine, zimelidine and amoxapine produced significant decreases in pHPG excretion which were much larger than those found in the brain. However, bupropion, trazodone and mianserin had no significant effect on pHPG excretion. Chlorpromazine was the only one of these six drugs that produced a significant reduction in brain pHPG (to 45% of control) at 24 hr, whereas nonsignificant decreases were seen after treatment with amoxapine (to 68%), trazodone (to 69%) and mianserin (to 81%). Interestingly, this decrease in brain pHPG at 24 hr after chlorpromazine was somewhat greater than that at 4.5 hr (to 45% vs 57%, respectively).

None of the above drugs had any effect on the 24-hr excretion of MHPG, except for chlorpromazine, which reduced MHPG excretion to 59% of control (24.4 ± 1.8 vs 41.5 ± 3.2 μg/24 hr; $P < 0.005$). Brain MHPG levels were unchanged by all of these drugs 24 hr after their injection.

DISCUSSION

The results show, like our previous studies of imipramine [1, 2], that several (but not all) other antidepressants decreased the concentrations of pHPG in brain and of tyrosine in brain and plasma.

Table 2. Drug effects on the 24-hr urinary excretion and brain levels of pHPG

Treatment	Urine pHPG (μg/24 hr) (% of control)	P	Brain pHPG (ng/g) (% of control)	P
Experiment 1				
Saline	1.82 ± 0.19 (100%)		2.60 ± 0.42 (100%)	
Chlorpromazine	0.347 ± 0.059 (19%)	<0.001	1.17 ± 0.07 (45%)	<0.02
Zimelidine	0.547 ± 0.116 (30%)	<0.001	2.33 ± 0.51 (90%)	NS
Bupropion	1.24 ± 0.27 (68%)	NS	2.99 ± 0.48 (115%)	NS
Experiment 2				
Saline	1.05 ± 0.30 (100%)		2.85 ± 0.59 (100%)	
Amoxapine	0.336 ± 0.102 (32%)	<0.05	1.95 ± 0.69 (68%)	NS
Trazodone	0.938 ± 0.162 (89%)	NS	1.97 ± 0.54 (69%)	NS
Mianserin	1.12 ± 0.09 (107%)	NS	2.30 ± 0.60 (81%)	NS

Rats (five/group) weighing 190–200 g (Expt. 1) or 240–250 g (Expt. 2) when received were fed a casein diet 1 week prior to administering the drugs, since constituents of standard lab chow elevate urinary pHPG excretion [1]. Urine was collected in receptacles containing 5 mg of sodium metabisulfite. The rats were killed by decapitation 24 hr after injection, and the brains were then assayed as described in the text. NS = not significant.

Amitriptyline, amoxapine, desmethylimipramine and iprindole in doses of 20 mg/kg and bupropion in a dose of 50 mg/kg each significantly lowered both plasma tyrosine levels after 1.5 hr and brain pHPG after 4.5 or 6 hr. Each of these drugs also reduced brain tyrosine after 1.5 hr, but the decreases were in every case smaller than for plasma tyrosine and reached statistical significance only for imipramine, amitriptyline and amoxapine. On the other hand, trazodone, trimipramine and amitriptylinoxide had no apparent effects, while mianserin (except for a significant decrease in plasma tyrosine) and zimelidine produced nonsignificant decreases in both pHPG and tyrosine. Since high doses of acute injections of zimelidine and amitriptyline (50 mg/kg) have been reported to lower mouse striatal *p*-tyramine concentrations [13], which in view of the present data most likely reflect diminished tyrosine concentrations, a higher dose of zimelidine than used in the present study would probably significantly lower both pHPG and tyrosine levels.

Although the decreases in brain pHPG and plasma tyrosine caused by antidepressants were correlated significantly ($r = 0.624$; $P < 0.05$), a causal relationship between these changes is not clear. A decrease of tyrosine in plasma could result in a diminished uptake of the amino acid into the brain and subsequently in a decrease in the flux of the pathway for tyrosine → tyramine → octopamine → pHPG. However, the results show that the decreases in tyrosine in brain were much smaller than those in plasma and were not correlated significantly with brain pHPG. Even the reductions of tyrosine in plasma were much smaller than the reductions in brain pHPG. Moreover, the decreases in pHPG persisted for at least 24 hr ([1]; Table 2), whereas tyrosine levels generally had returned to control levels by 4–6 hr ([2]; Table 1). Therefore, even though the reductions in both pHPG and tyrosine may be caused by a common (or similar) mechanism(s), it is clear that the decreases in pHPG cannot be due entirely to a lack of tyrosine availability. Studies with imipramine have shown that this antidepressant blocks the elevation in brain pHPG produced by tyrosine loading, suggesting that antidepressants can cause a decline in pHPG levels at least partly by inhibiting the conversion of tyrosine to pHPG [2].

Correlations between alterations in pHPG and tyrosine with *in vitro* inhibition of NE uptake suggest a possible role of noradrenergic mechanisms. One possibility is that, by blocking NE uptake, these drugs enhance the amount of NE within the synaptic cleft and thereby stimulate certain adrenoceptors (e.g. β-adrenergic receptors) which regulate tyrosine levels and/or octopamine turnover. Evidence supporting the idea that antidepressants regulate plasma tyrosine by stimulating adrenoceptors is provided by the finding that the peripherally active β-agonist, isoproterenol, lowers plasma tyrosine concentrations [14, 15]. However, the decreased levels of tyrosine in the brain induced by antidepressants cannot be due to an activation of peripheral β-adrenergic receptors, since isoproterenol raises rather than lowers brain tyrosine [14]. Moreover, it seems unlikely that the reductions in brain tyrosine caused by antidepressants are due to stimulation of β-receptors within the central nervous system, since salbutamol, a β_2-agonist that has both behavioral [16] and antidepressant effects [17], lowered plasma but not brain tyrosine.* The possibility that brain tyrosine levels

* D. J. Edwards and D. A. Sorisio, *Life Sci.* **42**, 853 (1988).

are regulated by β_1-adrenergic receptors, however, cannot be excluded.

The possibility that noradrenergic systems are involved in regulating octopamine metabolism is further suggested by the correlation between the decreases in pHPG and DHPG levels produced by various antidepressants (Fig. 1). This correlation probably is related to the ability of these drugs to block NE uptake and/or octopamine uptake [18]. Since DHPG is preferentially formed intraneuronally [19], drugs blocking NE uptake would be expected to lower DHPG formation. In contrast, MHPG is formed extraneuronally [19], and its levels therefore would reflect changes in NE release as well as uptake.

Consequently, various antidepressants can exert different effects on MHPG that cannot be predicted based on their potency of uptake inhibition alone. For example, mianserin elevated MHPG without increasing DHPG (Table 1). The ability of mianserin to raise MHPG confirms the work of Sugrue [20] and is presumably due to the yohimbine-like property of the drug in blocking α_2-adrenoceptors [21]. Our data (Table 1) suggest that amitriptyline may have a similar but weaker action. Although other investigators have not observed any significant increases in brain MHPG after amitriptyline [22, 23], Baumann and Maitre [24] did find evidence that amitriptyline blocked α_2-adrenoceptors based on an increase in [^{3}H]NE release from stimulated rat cortical slices. A similar disparity in effects on MHPG and DHPG was observed when yohimbine and desmethylimipramine were combined; whereas yohimbine alone raised both MHPG and DHPG, treatment with desmethylimipramine prior to yohimbine abolished the elevation in DHPG but enhanced the increase in MHPG [25].

What the relationship is between octopamine metabolism and NE uptake systems cannot be answered at present. Octopamine has been postulated to serve as a false transmitter [26] or a cotransmitter [27] in NE neurons. A depletion in pHPG could be explained by antidepressants blocking octopamine uptake into NE neurons, as has been demonstrated previously *in vitro* for desmethylimipramine by Baldessarini and Vogt [18]. Thus, following its release octopamine would be converted extraneuronally preferentially to the acidic metabolite, *p*-hydroxymandelic acid, rather than to pHPG. However, our finding that yohimbine has no influence on brain pHPG argues against the notion that significant amounts of octopamine are released from NE neurons [28].

Alternatively, antidepressants may diminish pHPG by acting on specific "octopaminergic" neurons. While there is no direct evidence for the existence of such neurons in the mammalian brain, the presence of octopamine-containing neurons in several invertebrates has been well established (reviewed in Ref. 29), and there is some indirect evidence to support the idea of such neurons in rat brain. For example, octopamine applied iontophoretically to single cortical neurons in the rat produced electrophysiological responses opposite to those caused by either NE or DA [30]. More recently, Duffield *et al.* [31] have provided further evidence for the existence of specific octopamine neurons in rat brain by showing that chlordimeform but not clonidine decreased octopamine turnover in the hypothalamus. If they do exist, octopamine neurons likely would have a re-uptake system with pharmacological properties similar to those of NE neurons, because of the structural similarities between octopamine and NE. In fact, marked similarities have been found for the high-affinity system for octopamine uptake in the cockroach CNS with the NE uptake system in mammalian tissues, including the inhibition of both systems by tricyclic antidepressants [32]. Such a similarity could explain the correlation between decreases in brain pHPG and NE uptake inhibition without any involvement of NE neurons.

The functional significance of the effects of antidepressants on tyrosine and octopamine metabolism remains to be determined. However, the present studies indicate that these effects are not generalizable to all antidepressants. Although these results could be viewed as an argument against a common mechanism for the therapeutic actions of these drugs, all antidepressant agents may not act by a common mechanism [20]. It is possible that certain antidepressants act by a mechanism involving tyrosine or octopamine but others work differently.

Our findings additionally indicate that the effects we have observed are not limited to antidepressants but also occur with the neuroleptic agent, chlorpromazine. The present data show that chlorpromazine lowered brain pHPG to 51% of control after 4.5 hr, which is virtually identical to the decrease to 52% produced by imipramine (Table 1). Moreover, chlorpromazine reduced the excretion of pHPG in the 24-hr period following injection to 19% of control and the brain level 24 hr after injection to 45% (Table 2). By comparison, previous work showed that imipramine lowered 24-hr pHPG excretion to 24% and brain pHPG 24 hr after injection to 62% [1]. We have shown that chlorpromazine also decreases brain and plasma tyrosine concentrations, to 57 and 42% respectively [3]. Taken together, these results indicate that chlorpromazine has at least equal if not more potent effects on tyrosine and pHPG than does imipramine.

However, these findings are not surprising in view of the fact that chlorpromazine shares in common with many antidepressant drugs several other pharmacological properties which have been thought to be associated with the mechanism of action of antidepressants. For example, chlorpromazine is approximately equipotent to imipramine in its inhibition *in vitro* of NE uptake [7]. Moreover, a loss in sensitivity of the NE-stimulated cyclic AMP system in rat brain, which is considered a common feature of chronic treatment with most antidepressant agents [33], occurs as a result of long-term treatment with chlorpromazine as well as with tricyclic antidepressants [12]. Similarly, studies from Meltzer's laboratory indicate that imipramine and chlorpromazine are approximately equally effective after a 2-week treatment in reducing the density of serotonin-2 receptor sites in the rat cerebral cortex [34] and in decreasing the number of [^{3}H]imipramine binding sites in rat frontal cortex and blood platelets

[35]. While such findings might argue against these biochemical changes as being relevant to the clinical effects, these results are consistent with some clinical evidence suggesting that phenothiazines have antidepressant properties [36, 37].

The apparent correlation between desensitization of the NE receptor coupled adenylate cyclase system and the reduction in brain pHPG is intriguing. This is especially so because the effects on the cyclase occur only after chronic treatment which, due to the delay in therapeutic action, is thought to be more relevant to the clinical situation [33], whereas the effects on brain pHPG occur after a single treatment. It is possible that a reduction in octopamine turnover (or a related metabolic change) after an acute treatment perhaps acts to trigger changes in receptor sensitivity that appear after long-term treatment.

At present no single pharmacological property can adequately explain how antidepressants act. Different drugs may act through different mechanisms [20]. An alternate hypothesis is that these drugs simultaneously affect multiple systems which act synergistically to produce a therapeutic effect. Perhaps a reduction in tyrosine levels or octopamine turnover represents one condition which when combined with one of the other actions (or absence of particular actions) of the drugs results in the antidepressant effect. On the other hand, reductions in tyrosine or pHPG may represent unwanted effects of an antidepressant. If so, supplementation with tyrosine or switching to an antidepressant without tyrosine-depleting effects could be beneficial in treating non-responders to a particular drug. In this context, it is interesting to note that tyrosine has been found, in a small number of patients, to alleviate depression [38].

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