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Inhibition of phenylethylamine metabolism *in vivo*—Effect of antidepressants

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Despite the widespread use of tricyclic antidepressants, the mechanism of their antidepressant action remains unclear. Although it is widely acknowledged that the blockade of norepinephrine uptake may be a contributing factor [1], this mechanism is not exclusive of non-antidepressants nor is it inclusive of all tricyclic antidepressants [2]. In the search for an alternative mechanism, Fischer *et al.* [3] and Mosnaim *et al.* [4] have examined the effects of imipramine on brain phenylethylamine levels. They found that this putative ergotropic modulator was increased in rat brain after imipramine treatment and suggested that this elevation might be related to antidepressant efficacy. Although Fischer *et al.* did not determine the mechanism involved in the imipramine-induced elevation of phenylethylamine, recent experiments *in vitro* [5, 6] have indicated that tricyclic antidepressants may block the deamination of phenylethylamine by type B monoamine oxidase. The present experiments were designed to determine if antidepressants alter the metabolism of phenylethylamine *in vivo* at non-toxic doses.

Male mice (CF-1) or rats (Sprague–Dawley) were treated with several monoamine oxidase inhibitors and tricyclic antidepressants, either acutely or chronically, prior to intravenous administration of [^{14}C]β-phenylethylamine ([^{14}C]PEA, New England Nuclear, 9·86 mCi/m-mole). In the initial acute mouse study, compounds were injected intraperitoneally (i.p.) 1 hr before the labeled amine. In the chronic study, groups of four mice were placed on a diet containing 0·05% of one of several antidepressants for 1 week before receiving [^{14}C]PEA. Rats used in this study received one dose i.p. of either 50 mg/kg of pargyline or imipramine 24 hr prior to injection with the labeled amine. All mice received 0·1 μCi of [^{14}C]PEA and rats received 1 μCi. Ten min after the radioactive amine was injected, the animals were sacrificed by decapitation, and the brains were removed and placed on dry ice. The tissues were homogenized in 2 vol. of 0·1 N HCl, and 1 vol. of 30% $HClO_4$ was added [7]. After precipitated protein was removed by centrifugation, the pH of the supernatants was adjusted to above 11 with 10 N NaOH. One-ml aliquots were shaken for 10 min with 3 ml benzene and sufficient NaCl to saturate. Two and one-half ml of the benzene fraction was transferred and washed with 1 ml of 0·1 N NaOH and NaCl to saturate. Two ml of the washed benzene fraction was taken for radioactivity determination liquid scintillation spectrometry. The activity (cpm) was converted to dis./min using a correction factor obtained from counting a known amount of [^{14}C]PEA (counting efficiency = 86 per cent).

An acute single dose pretreatment of mice with standard monoamine oxidase inhibitors resulted in a large increase in [^{14}C]PEA brain levels (Table 1). However, similar treatment with the tricyclic antidepressants failed to alter the metabolism and disposition of [^{14}C]PEA.

Table 1. Effect of several monoamine oxidase inhibitors and antidepressants on metabolism *in vivo* of [^{14}C]phenylethylamine in mouse brain*

Drug	Dose (mg/kg)	[^{14}C]PEA (mean dis./min ± S. E. M.)
Control		69 ± 0
Pargyline	30	3605 ± 318
Tranylcypromine	30	7563 ± 389
Nialamide	30	1141 ± 78
Imipramine	30	69 ± 2
Iprindole	30	81 ± 7
Amitriptyline	30	71 ± 2

* Each figure is the result of four determinations. Drugs were administered intraperitoneally 1 hr before [^{14}C]PEA.

Table 2. Effect of chronic treatment with several antidepressants on metabolism *in vivo* of [^{14}C]phenylethylamine in mouse brain*

Drug†	Dose	[^{14}C]PEA (mean dis./min ± S. E. M.)
Control		66 ± 0
Imipramine	0·05% in diet	69 ± 2
Iprindole	0·05% in diet	71 ± 2
Amitriptyline	0·05% in diet	66 ± 2

* Each figure is the result of four determinations.
† Approximate dose = 75 mg/kg/day for 7 days.

Table 3. Effect of pargyline and imipramine on metabolism *in vivo* of [^{14}C]phenylethylamine in rat brain*

Drug	Dose (mg/kg)	[^{14}C]PEA (mean dis./min ± S. E. M.)
Saline		258 ± 7
Pargyline	50	6462 ± 282
Imipramine	50	263 ± 7

* Each figure is the result of four determinations. Drugs were given intraperitoneally 24 hr before [^{14}C]PEA.

Since the antidepressant effects of tricyclics are only apparent after several days of treatment, the effects of chronic dosing of tricyclics on [^{14}C]PEA metabolism was examined. The data in Table 2 indicate that, despite exposure to the drugs for 7 days, no alteration in [^{14}C]PEA metabolism was observed.

Species differences in monoamine oxidase activity have been noted. In the study of Fischer *et al.* [3], rats were used and a single dose of imipramine was given 24 hr before sacrifice. Therefore, the metabolism of [^{14}C]PEA *in vivo* was examined under similar conditions (Table 3). Again, as in the experiment with mice, imipramine pretreatment failed to alter [^{14}C]PEA brain levels, although pargyline was markedly active.

The parameter measured in these experiments (i.e. brain [^{14}C]PEA) might also be altered by a change in the distribution of [^{14}C]PEA to the brain. However, this is not the case with imipramine pretreatment. The amount of total radioactivity in the brains of rats pretreated with imipramine (19,834 ± 713 dis./min) does not differ significantly from that in the control brains (18,558 ± 799 dis./min). Similarly, the elevation in brain [^{14}C]PEA seen after pargyline treatment (1853 ± 164 dis./min) is not altered by co-treatment with imipramine (1903 ± 337 dis./min). Thus, imipramine neither blocks the distribution of [^{14}C]PEA into the brain nor the ability of pargyline to elevate [^{14}C]PEA levels. Furthermore, the use of exogenous [^{14}C]PEA to study metabolism of PEA in the brain is justified by the rapid penetration of PEA into the brain and by the observation that plasma PEA is a major source of brain PEA [8].

The data *in vivo* presented here are in sharp contrast to the conclusions of Roth and Gillis [5]. Their experiments *in vitro* indicated an inhibition of phenylethylamine deamination by tricyclics. In the absence of confirmation *in vivo* of this effect, we seriously question its importance to the pharmacological effects of tricyclic antidepressants. Thus, the elevation in apparent PEA in brain after imipramine treatment reported by Fischer *et al.* [3] cannot be explained by an inhibition of PEA metabolism.

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