Effects of tranylcypromine and pargyline on brain tryptamine[1]

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Summary. Tranylcypromine produces behavioral excitation while pargyline produces depression. Tranylcypromine increased brain tryptophan which led to an accumulation of tryptamine. The levels of tryptamine after tranylcypromine were found to be 3 times those found after pargyline.

The presence of tryptamine in the CNS of animals and humans has been demonstrated by several authors[5-8] and the possible involvement of this amine in the etiology of affective illness has been hypothesized[9]. Recently the work of Foldes and Costa[10] and that of our laboratory[11] has focused attention on the possibility that tryptamine may be responsible for the behavioral syndrome which becomes apparent after the administration of tryptophan in the presence of a monoamine oxidase inhibitor (MAOI). This syndrome includes hyperactivity and hyperthermia[10-12] and can also be elicited by the injection of tranylcypromine without concomitant tryptophan loading. In a previous publication[11] we demonstrated that tranylcypromine raised the endogenous levels of tryptophan in mouse brain and we proposed that such increases in brain tryptophan levels would promote the formation of tryptamine in brain. Therefore, it was of interest to monitor the effects of tranylcypromine on brain tryptamine levels. Pargyline was used for comparative purposes.

Methods. (±)-Tranylcypromine was purchased from Sigma Chemical Company. Pargyline was supplied by Saber Laboratories and L-tryptophan was supplied by Calbiochem. Male C57B1/6 mice, purchased from ARS Sprague Dawley, were used as experimental animals. All studies were initiated at 10.00 a.m. and performed at an ambient temperature of 22 ± 1 °C. Drugs were administered i.p. in isotonic saline in a volume of 0.1 ml/10 g body weight. Mice were decapitated 45 min after the injection of saline or the MAOI, since we had found that brain tryptophan levels peak at this time after the administration of tranylcypromine[11]. Tryptophan, when used, was injected 15 min after pargyline administration and the animals were sacrificed 45 min after the administration of the MAOI. Brains of all animals were quickly removed and weighed within 60 sec of decapitation and immediately frozen on dry ice.

Analysis of tryptamine and p-tyramine in the brains was initiated within 24 h after death. They were determined after their isolation from tissue by mass spectral analysis as their dansylated derivatives[6,13]. Internal standards (deuterated p-tyramine and tryptamine) were added to tissue homogenates at the commencement of the isolation and analysis, and the integrated ion current profile obtained from the appropriate molecular ions was used to calculate the amount of amine present[6,13].

Results. Levels of tryptamine found in brains of mice injected with saline (table) were similar to those previously reported to be present in rat brain[7]. The administration of pargyline (100 mg/kg) produced a 36fold increase in brain tryptamine levels (table). Tryptamine levels in tranylcypromine-pretreated animals were found to be 96fold greater than those of control animals and significantly ($p < 0.001$) greater than those of the animals receiving pargyline. The administration of tryptophan to animals pretreated with pargyline was, however, found to result in a significant further increase in brain tryptamine compared to animals receiving only pargyline (table).

Although the levels of p-tyramine were raised more than 2fold by the administration of MAOI's, no significant differences in levels of this amine were found between animals treated with tranylcypromine, pargyline or pargyline and tryptophan ($p > 0.05$).

Discussion. Our previous work[11] demonstrated an equivalent inhibition of monoamine oxidase (using substrates for both A and B forms of the enzyme) and similar rates of accumulation of serotonin in brains of animals treated with either tranylcypromine or pargyline. Although serotonin levels in the brains of both the tranylcypromine and pargyline treated animals were similar (~40% increase) after 45 min, the behavioral profile of the animals was significantly different[11]. The animals treated with tranylcypromine were hyperactive while the general activity of those animals receiving pargyline was depressed. Such results have also been reported by others[10]. Since tranylcypromine was found to elevate brain tryptophan levels while pargyline did not[11], we postulated that, considering the kinetic characteristics of tryptophan hydroxylase and aromatic amino acid decarboxylase, tryptophan may be decarboxylated to tryptamine, and tryptamine would be responsible for some of the behavioral effects seen after tranylcypromine administration. Our current work demonstrated a significantly greater increase in tryptamine level in brains of tranylcypromine-treated animals compared to those treated with pargyline.

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Brain tryptamine and tyramine after treatment with MAOI's and tryptophan

Treatment	Amine levels (ng/g brain) Tryptamine	p-Tyramine
Saline	0.19±0.04	3.24±0.29
Tranylcypromine (25 mg/kg)	18.20±2.21*	7.94±0.68
Pargyline (100 mg/kg)	6.93±1.29	6.80±0.49
Pargyline (100 mg/kg) and tryptophan (50 mg/kg)	32.70±5.55*	6.99±0.94

Amine levels were determined as noted in the text. Control values were derived from 4 groups of saline-injected mice: each group consisted of brains from 7 animals. Each of the other values was calculated from 5 groups of animals; each group consisted of 5–7 brains. Values are means ± SD.

* Significantly greater compared to pargyline-treated animals, $p < 0.001$, t-test.

Tryptamine administration has been shown to produce hyperactivity in rats[10] and recent work by Marley and Nistico[14] has demonstrated that behavioral arousal after systemic administration of tryptamine[14,16] is due to tryptamine's action in the CNS. Tryptamine has also been shown to act within the CNS and produce facilitation of spinal reflexes[17]. Thus, certain behavioral and physiologic concomitants of the administration of tranylcypromine may be mediated by the associated increases in brain tryptamine levels.

On the other hand, the pharmacologic effects of tranylcypromine may be mediated, primarily, by direct interaction of this drug with catecholaminergic neurons. Tranylcypromine is a structural analogue of amphetamine and has been shown to release[18] and block the uptake[18,19] of norepinephrine. Previous work by Foldes and Costa[10] demonstrated the necessity of catecholaminergic systems in the expression of the tranylcypromine-induced syndrome of hyperactivity since pretreatment of the animals with 6-hydroxydopamine blocked the appearance of the syndrome. It is however possible that the increased tryptamine levels produced by tranylcypromine administration may also affect catecholamine neurons (eg., by promoting release). Our postulate that some of the effects of tranylcypromine are mediated by the increased brain tryptamine levels is further supported by the observations[10] that the behavioral depression seen in pargyline-treated animals could be reversed by concomitant administration of tryptophan which we have demonstrated to further raise the brain tryptamine levels in the pargyline-pretreated animals (table). However, since increases in brain tryptamine levels after administration of pargyline alone (see table) did not result in behavioral arousal, it is evident that relatively large increases in brain tryptamine levels would be necessary to obtain pharmacologic effects. These effects could be more evident in the presence of a diminished uptake of the catecholamine transmitters in the presence of tranylcypromine. Pargyline in contrast to tranylcypromine has little effect on blockade of catecholamine uptake[18,19].

Pargyline and tranylcypromine did not exhibit differential effects on the levels of p-tyramine in brain, and one may suppose that tyrosine levels are not differentially affected by these MAOI's. One should, however, consider that p-tyramine can be formed in brain by hydroxylation and dehydroxylation of phenylethylamine and dopamine as well as by the primary decarboxylation of tyrosine[20–22]. Tranylcypromine is used clinically as an antidepressant[23], and the beneficial effects of this drug have been ascribed to its actions in blocking the uptake of catecholamines[19] as well as its action as an MAOI. However, the effect of tranylcypromine on brain tryptamine levels had not previously been investigated. Tryptamine output in the urine of depressed patients has been claimed to be below the levels found in normal individuals, and these levels were reported to return to the normal range upon remission of the illness[9]. Several reports[24,25] have also claimed that the treatment of depression by a combined therapy with tryptophan and MAOI is superior to MAOI alone. Our results on the effects of tranylcypromine and pargyline plus tryptophan on increasing brain tryptamine levels should encourage a further examination of the role of this amine in the etiology of depressive illness and its remission.

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