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LETTERS TO THE EDITOR

Peripheral factors in the mediation of the effects of L-dopa on locomotor activity

Injection of 3,4-dihydroxyphenylalanine (dopa), the metabolic precursor to dopamine, noradrenaline, and adrenaline, produces pronounced autonomic symptoms such as salivation, piloerection, exopthalamus, and elevated blood pressure and respiratory rate (Blaschko & Chrusciel, 1960; Smith & Dews, 1962; Marley, 1966) and also has been reported to both increase and decrease locomotor activity. Smith & Dews (1962) described some of the autonomic effects mentioned above and found that DL-dopa decreased spontaneous motor activity in doses ranging from 100–1000 mg/kg. In contrast, Blaschko & Chrusciel (1960) reported increases in motility after L-dopa in doses greater than 500 mg/kg. Boissier & Simon (1966) found that DL-dopa in lower doses ($<$500 mg/kg) suppressed locomotor activity but caused hyperkinesia at 1000 mg/kg. Further, several authors have reported suppression of various types of conditioned behaviour after dopa (Eiduson, 1959; Boff & Heise, 1963; Scheckel, Boff & others, 1965). The excitatory effects of dopa are thought to be mediated centrally, probably by the catabolites dopamine and noradrenaline (Carlsson, 1965). To our knowledge, however, no explanations have been given for the suppression of spontaneous motor activity and conditioned behaviour observed particularly after lower doses.

In a previous paper (Butcher & Engel, 1969) we reported that if the enzyme dopa decarboxylase was selectively inhibited in the periphery by 50 mg/kg Ro 4–4602 (seryltrihydroxybenzylhydrazine), then a subsequent injection of L-dopa produced only excitatory effects (i.e. increase in lever-pressing rate on a free-operant avoidance schedule). At the dose of Ro 4–4602 used, only peripheral decarboxylase activity is inhibited whereas the enzyme in brain is relatively unaffected (Bartholini & Pletscher, 1968). Since in our experiments the autonomic effects of dopa were absent after peripheral decarboxylase inhibition, we suggested that the suppressant effects on behaviour reported by some investigators may have been attributable to the action of physiologically active dopa catabolites in the periphery. We now present further evidence for this view.

Sixty male Sprague-Dawley rats, ~200 g weight, had their individual motor activities recorded every 5 min for 1 h, in activity boxes described by Svensson & Thieme (1969). The drugs studied were (doses are expressed in terms of the drug forms shown): L-dopa, 150 mg/kg; dopamine HCl, 150 mg/kg; and Ro 4–4602, 50 mg/kg. In addition to investigating the effects of these drugs alone, we also examined the effects on locomotor activity of Ro 4–4602 in combination with dopa and of dopamine in rats pretreated with Ro 4–4602 and dopa. The drugs were intraperitoneally administered at the following times before the start of the testing session: L-dopa, 45 min; dopamine, 5 min, and Ro 4–4602, 75 min. In the regimen in which the effects of dopamine were studied after prior treatment with Ro 4–4602 and dopa, the dopamine was injected 10 min after the start of the session. Each drug-treatment group consisted of 10 rats. The results were statistically evaluated using analysis of variance with a P $\times$ Q factorial design (Winer, 1962). *A posteriori* analyses comparing each treatment condition with every other were performed using the Newman-Keuls procedure (Winer, 1962). A $P < 0{\cdot}05$ was arbitrarily required for significance.

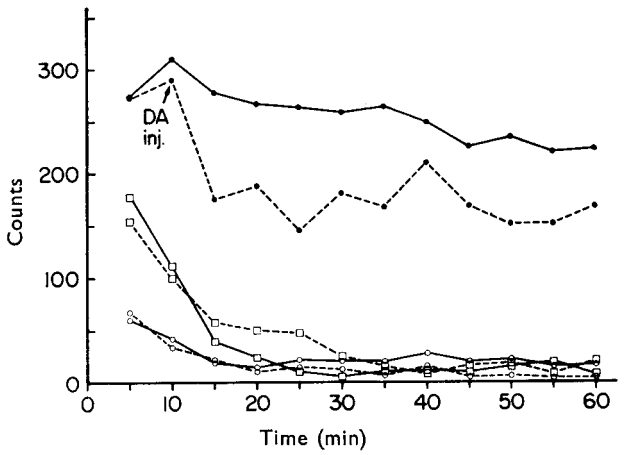

FIG. 1. Effects on locomotor activity of each drug regimen. The doses and time of injection before the start of session are as follows: Ro 4–4602, 50 mg/kg, 75 min; L-dopa, 150 mg/kg, 45 min; dopamine (DA), 150 mg/kg, 5 min. In the Ro 4–4602-dopa-dopamine regimen, the time of dopamine administration is indicated at the arrow. Each point represents the mean of 10 values. Ro 44602 + L-dopa ●—●. Ro 44602 + L-dopa + dopamine ●— —●. Control □—□. Ro 44602 □— —□. L-Dopa ○—○. Dopamine ○— —○.

No significant differences were found between control levels of performance and motor activity after Ro 4–4602 at any of the time intervals (Fig. 1). But dopa and also dopamine significantly reduced ($P < 0{\cdot}01$, compared to control) locomotor activity at the 5 and 10 min intervals (Fig. 1). This is consistent with the results of Smith & Dews (1962). No significant differences were found at the remaining time intervals due to the fact that control activity itself decreased at later portions of the session (Fig. 1). Dopa and dopamine also produced marked automatic symptoms characterized primarily, as assessed by gross observation, by piloerection, salivation, and exopthalmus.

In agreement with the recent findings of Bartholini, Blum & others (1969), dopa in combination with Ro 4–4602 caused an increase in spontaneous motor activity (Fig. 1) and also stereotyped movements of the head and forepaws. In contrast to dopa and dopamine alone, no autonomic manifestations were observed. Locomotor activity was significantly increased over control ($P < 0{\cdot}01$) at all time intervals measured. Introduction of peripheral symptoms by an injection of dopamine in rats pretreated with Ro 4–4602 and dopa was correlated with a significant decrease ($P < 0{\cdot}05$) in motor activity, compared to the Ro 4–4602 dopa treatment, at all time intervals following dopamine administration except the 40 min interval (Fig. 1). Before dopamine injection, no significant difference was found between the Ro 4–4602-dopa animals and the Ro 4–4602-dopa-dopamine group. At all time intervals, however, the activity under the Ro 4–4602-dopa-dopamine regimen was significantly increased over control ($P < 0{\cdot}01$). In addition, 5 of the 10 rats died within 3 h after receiving Ro 4–4602, dopa, and dopamine, whereas no animals died after the other drug treatments. This latter finding suggests that central stimulation may contribute to the lethal effects Ro 4–4602 and of dopa in combination with dopamine.

The dopa-induced suppression of locomotor activity observed in our experiments was probably attributable to physiologically active dopa catabolites in the periphery, although the precise mechanism for this effect is unknown. The following data are compatible with this contention: since the behavioural and autonomic effects of dopa can be blocked after combined central and peripheral decarboxylase inhibition and potentiated after monoamine oxidase inhibition, dopa itself is thought to be

pharmacologically inert and its effects mediated by the catecholamines formed from it at different central and peripheral sites (Carlsson, 1965). Further, injection of dopamine in our experiments produced the same autonomic signs as after dopa, and locomotor activity was suppressed to approximately the same extent. Noradrenaline and adrenaline administration has also been found to suppress conditioned behaviour in pigeons and cats (Sharpless, 1955; Wurtman, Frank & others, 1959). Since catecholamines do not appreciably cross the blood-brain barrier (Weil-Malherbe, 1960), these effects are probably due to actions at peripheral sites. When extracerebral dopa decarboxylase was inhibited in our experiments, L-dopa produced marked stimulation of locomotor activity without autonomic symptoms. A subsequent injection of dopamine in these latter animals resulted in a decrease in motor activity which was accompanied by marked autonomic manifestations. It is possible, therefore, that when dopa is injected alone, catecholamines are preferentially formed in the periphery; their action at peripheral sites may therefore mask the effect of the centrally formed amines. The fact that the enzyme dopa decarboxylase has a higher activity extracerebrally than in the brain (Blaschko & Chrusciel, 1960) supports this view.

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