Effect of protriptyline on the formation of [^{3}H]noradrenaline from [^{3}H]dopa

SIR,—Protriptyline, like other imipramine-like antidepressive agents, has been shown to block the amine-uptake mechanism at the level of the cell membrane of the peripheral (Carlsson & Waldeck, 1965; Malmfors, 1965) and central noradrenaline-storing neurons (Carlsson, Fuxe & others 1966). It has not been possible, however, to block the uptake mechanism of the dopamine neurons in the brain by members of this group of drugs (Carlsson & others 1966; Hamberger 1968). Further it has been shown that desipramine and protriptyline are able to reduce the accumulation of noradrenaline after dopa in both central and peripheral noradrenaline-neurons of reserpine, and nialamide-pretreated animals (Carlsson & others 1966). The present investigation was made to clarify the interaction of protriptyline with central and peripheral adrenergic mechanisms using [^{3}H]dopa in doses too low to influence the levels of the endogenous catecholamines.

Female mice, grouped six by six, were given 5 μg/kg [^{3}H]dopa with a specific activity of 33 c/mmole. In some experiments 10 mg/kg protriptyline was given 15 min before the [^{3}H]dopa, in others 15 min after. All injections were made intravenously. One hr after the injection of [^{3}H]dopa the animals were killed by decapitation, their hearts and brains removed and analysed for [^{3}H]noradrenaline and [^{3}H]dopamine as described elsewhere (Persson & Waldeck,1968).

When protriptyline was given 15 min before the [^{3}H]dopa, the yield of [^{3}H]noradrenaline from brain was three times lower than in the controls, whereas [^{3}H]dopamine increased about 60% (Fig. 1A). Pretreatment with protriptyline also reduced the yield of [^{3}H]noradrenaline from heart by about three times; [^{3}H]dopamine in this organ showed, if anything, a decrease. Protriptyline given 15 min after [^{3}H]dopa had little or no effect on [^{3}H]noradrenaline and [^{3}H]dopamine in brain or heart.

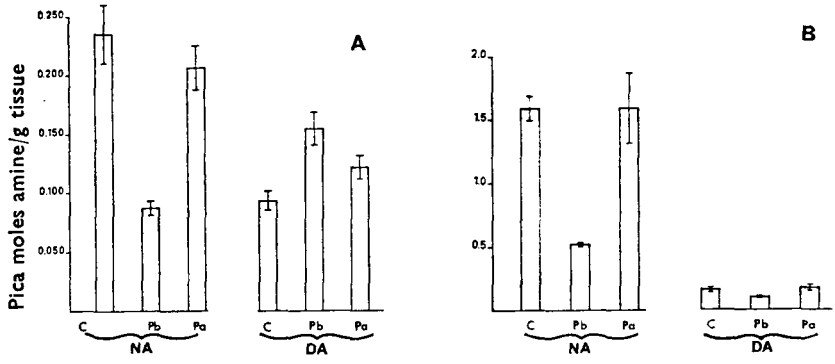

FIG. 1. Influence of protriptyline on formation in the mouse brain (A) and in the mouse heart (B) of [^{3}H]noradrenaline and [^{3}H]dopamine from [^{3}H]dopa. The controls C received [^{3}H] dopa (5 μg/kg i.v.) 60 min before being killed. The second experimental group (Pb) received protriptyline (10 mg/kg i.v.) 15 min before [^{3}H]dopa. The third group (Pa) received the same dose of protriptyline 15 min after [^{3}H]dopa. Each value is the mean of 3 experiments, each on 6 mice, whose brains and hearts, respectively, were pooled. Means $\pm$ s.e. are shown.

Reduced accumulation of noradrenaline with a concomitant increase in the dopamine level might indicate inhibition of the dopamine-β-hydroxylase. That protriptyline should block this enzyme does not seem very likely since the imipramine-like agents do not seem to possess dopamine-β-hydroxylase inhibiting properties *in vitro* (Creveling, Daly & others 1962). Furthermore, in the animals treated with protriptyline 15 min after [^{3}H]dopa, synthesis of [^{3}H]noradrenaline appeared to proceed undisturbed, the concentration of this amine being approximately doubled between 15 and 60 min after administration of [^{3}H]dopa (*cf.* Persson & Waldeck, 1968). This observation seems hard to reconcile with the assumption of an inhibition of dopamine-β-hydroxylase.

A more likely interpretation of the protriptyline effects observed seems to be interference by the drug with the transport of the dopamine serving as noradrenaline precursor. Carlsson & others (1966) proposed that in their experiments the "membrane pump blocker" desipramine prevented dopamine, formed after injection of dopa to animals pretreated with reserpine and nialamide, from re-uptake into the noradrenaline neurons after it had leaked out through the cell membrane. The now reported effects of protriptyline may be interpreted in similar manner. During the first minute after injection of [^{3}H]dopa the precursor will reach the dopa-decarboxylase near the cell membrane. The [^{3}H]dopamine formed has great opportunity to leak out but is taken up again by the "membrane pump". If protriptyline is given before [^{3}H]dopa this re-uptake is blocked and [^{3}H]noradrenaline levels in brain and heart will fall. The [^{3}H]dopamine outside the cell membrane of the central noradrenaline neurons cannot be transported away by the circulation, being prevented by the blood-brain barrier, but at the peripheral neurons this transport is possible. This may explain why [^{3}H]dopamine in brain, but not in heart, rose after protriptyline pretreatment. When protriptyline is given 15 min after [^{3}H]dopa, the [^{3}H]dopamine formed may be distributed more evenly in the cytoplasm, and leakage may thus be of less importance. Therefore the protriptyline effect on [^{3}H]dopamine and [^{3}H]noradrenaline is greatly reduced.

While studying the time-course of [^{3}H]catecholamine formation in mice from [^{3}H]dopa we have found an early accumulation of [^{3}H]dopamine with a maximum at 7½ min in brain and at 15 min in heart (Persson & Waldeck, 1968). As discussed in our previous paper, this accumulation might be extraneuronal, which would be in line with the interpretation given above. The recently reported findings by Nybäck & Sedvall (1968) that desipramine blocked the accumulation of [^{14}C]noradrenaline when given before but not after the precursor [^{14}C]tyrosine might be explained in similar manner.

The possibility of an extraneuronal decarboxylation of [^{3}H]dopa and an inhibition by protriptyline of the uptake of the [^{3}H]dopamine formed into the noradrenaline neurons may also be considered. However, against this possibility is the fact that most of the dopa decarboxylase activity seems to be located intraneuronally. For the central nervous system this has been demonstrated by Andén, Magnusson & Rosengren (1965), Heller, Seiden & others (1965) and Andén, Dahlström & others (1966). It is thus unlikely that the dopa decarboxylation occurring in the capillary walls (see Owman & Rosengren, 1967) is of any considerable importance for providing dopamine-β-hydroxylase with substrate.

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The effect of methylcellulose on the absorption of nitrofurantoin from the gastrointestinal tract

SIR,—Although many pharmaceutical suspensions are viscous, little attention has been paid to the relation between viscosity and the absorption of insoluble drugs from the gastrointestinal tract.

The relation has already been noted with soluble drugs. Malone, Gibson & Miya (1960), for example, noted that an increase in the concentration of sucrose in aqueous solutions of sodium phenobarbitone considerably lengthened the induction time for narcosis. Davison, Guy & others (1961) found that the plasma and brain salicylate levels after the oral administration of sodium salicylate solutions were significantly reduced when methylcellulose was added to the formulation. Recently, Levy & Jusko (1965) showed that methylcellulose reduced the uptake of salicylic acid from ethanol–water mixtures by the ligated rat stomach.

I have found that the insoluble urinary antiseptic nitrofurantoin when dispersed in therapeutically realistic volumes in methylcellulose and taken by mouth, is not excreted as rapidly in the urine as the drug in water suspension.

Freshly prepared suspensions of 0·5% w/v nitrofurantoin in water were administered (1·5 mg/kg) to 9 healthy male volunteers after an overnight fast. This was followed by 100 ml water. The bladder was emptied and urine was collected at hourly intervals. The procedure was repeated with 0·5% w/v nitrofurantoin suspensions in 5% w/v methylcellulose solutions. All urine samples were assayed immediately after collection by a polarographic method described by Jones, Ratcliffe & Stevens (1965).

The effect of methylcellulose on the excretion rate of nitrofurantoin is shown in Fig. 1. In the presence of methylcellulose, the concentration of nitrofurantoin in urine rises less rapidly and the peak concentration is delayed by 1 hr. The