Synergistic elevation of brain 3,4-dihydroxyphenylacetic acid concentration by methylphenidate and spiperone in control but not reserpine-pretreated rats

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Shore (1976) reported that amfonelic acid acted synergistically with a dopamine receptor blocking drug to elevate 3,4-dihydroxyphenylacetic acid (DOPAC) concentration and increase dopamine turnover in rat brain. In contrast to amfonelic acid and certain other stimulant drugs (like methylphenidate and cocaine), a second group of stimulant drugs did not increase dopamine turnover in rats treated with a dopamine receptor blocker. This latter group included both stereoisomers of amphetamine and methamphetamine.

An explanation offered for the action of the methylphenidate-like drugs is that they facilitated the impulse-mediated release of dopamine, leading to greater accumulation of dopamine metabolites when the firing of dopamine neurons was increased as a compensatory response to dopamine receptor blockade (Shore 1976) Apparently, dopamine neurons contain a large storage pool of neurotransmitter that is not readily mobilized, and methylphenidate facilitates the mobilization of this pool. This line of reasoning would predict that reserpinization to deplete the dopamine storage pool would prevent the synergistic elevation of DOPAC by methylphenidate and a dopamine antagonist.

Methylphenidate (10 mg kg^{-1}) was injected into rats 1 h before they were killed and 1 h after they had been treated with spiperone (0·5 mg kg^{-1}), a potent dopamine receptor antagonist (Leysen et al 1978). Some rats were pretreated with reserpine (5 mg kg^{-1}) 5 h before they were killed. All drug injections were i.p. Rats were decapitated, and whole brains were removed and frozen on dry ice. DOPAC concentration was determined spectrofluorometrically according to Murphy et al (1969). Mean values ± standard errors for 5 rats per group were calculated, and comparisons between groups were made by the 2-tailed Student's *t* test.

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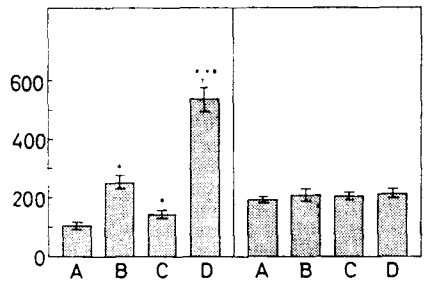

FIG. 1. Effect of (B) methylphenidate (C) spiperone alone and (D) in combination on brain DOPAC (ordinate: ng g^{-1}) in control rats (left panel) and in reserpine-pretreated rats (right panel). *Significant difference ($P<0·05$) from the control group in that panel; **significant difference ($P < 0·05$) from the groups treated with either methylphenidate or spiperone alone. A, control.

Fig. 1 (left panel) shows the effect of methylphenidate and spiperone on the short term DOPAC concentration in rat brain. Methylphenidate caused a slight but statistically significant increase in DOPAC. Spiperone caused a 2·5-fold increase in DOPAC, an increase that is maintained for several h after spiperone treatment (Fuller & Snoddy 1979). The combination of methylphenidate and spiperone caused a greater than additive elevation of brain DOPAC. The percentage increase in DOPAC concentration was 39% after methylphenidate, 141% after spiperone, and 407% after the drug combination. The synergism between methylphenidate and spiperone in elevating brain DOPAC was expected from the report by Shore (1976) that methylphenidate decreased dopamine concentration after inhibition of dopamine synthesis in haloperidol-treated rats.

DOPAC concentrations were elevated in reserpine-pretreated rats to nearly twice the control values (Fig. 1, right panel). Spiperone caused a slight but not statistically significant increase in brain DOPAC in these rats Methylphenidate alone or in combination with spiperone did not cause any significant increase in DOPAC. Thus in contrast to the 5-fold increase after the methylphenidate-spiperone combination in control rats, there was no significant effect on brain DOPAC in reserpinized rats. Braestrup (1977) had previously observed that methylphenidate alone did not elevate DOPAC in reserpine-pretreated rats.

The ability of reserpine, which is known to deplete dopamine stores, to prevent the synergistic elevation of brain DOPAC by methylphenidate and spiperone is compatible with the mechanism of action of methylphenidate suggested by Shore (1976). Normally methylphenidate facilitates the impulse-mediated release of dopamine storage pools to produce the increase in DOPAC, hence it cannot act in reserpinized rats lacking those storage pools.

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