Department of Physiology and Anatomy, J. C. NEWHOOK
Massey University,
Palmerston North,
New Zealand.

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Aggressive behaviour provoked by pargyline in rats pretreated with diethyldithiocarbamate

SIR,—We have previously described various forms of aggressive behaviour induced by drugs affecting the brain amines (Randrup & Munkvad, 1966; 1968).

An excitation characterized by fighting, vocalization together with sudden bursts of fast running was reported in experiments with rats treated with monoamine oxidase inhibitors + L-dopa, the physiological precursor of the catecholamines, dopamine and noradrenaline. Biochemically this behaviour was connected with high levels and turnover of dopamine and noradrenaline (Scheel-Krüger & Randrup, 1967).

The present paper deals with an aggressive behaviour induced by the monoamine oxidase inhibitor pargyline in rats pretreated with repeated doses of disodium diethyldithiocarbamate $2H_2O$ (DDC).

DDC inhibits the synthesis of brain noradrenaline by blockade of the enzyme dopamine-β-oxidase (Goldstein & Nakajima, 1966; Carlsson, Lindqvist & others, 1966).

Male Wistar rats weighing 225–275 g were used. Rats (22) were observed after four doses of DDC given subcutaneously; 18 hr after the first dose of 500 mg/kg, the rats received 500, 50 and 500 mg/kg subcutaneously at intervals of 2 hr.

Another 35 rats were given pargyline hydrochloride (150 mg/kg s.c.) 2 hr before the last DDC injection, while 21 rats received pargyline alone.

The brain content of dopamine, noradrenaline and their respective 3-*O*-methylated metabolites, 3-methoxytyramine and normetanephrine, was analysed by a method involving chromatographic separation of the amines followed by a fluorimetric determination (Scheel-Krüger & Randrup, 1967; Jonas & Scheel-Krüger, unpublished).

The rats treated with the four injections of DDC were already sedated (no spontaneous activity in the home cage) before the last dose of DDC. The sedation persisted for at least 6 hr.

A striking contrasting behavioural excitation of aggressive character was provoked by the additional dose of pargyline.

The aggressive behaviour began 4–5½ hr after pargyline and increased in intensity during the following 2–3 hr.

Bursts of spontaneous vocalization were sometimes heard from rats kept in individual cages. Two rats placed in the same cage reared face to face in defence posture striking at each other with their forelegs. Much vocalization was heard in this situation (26/35 rats showed this behaviour). Rats receiving pargyline only as a control did not show these aggressive features. Vocalization and stereotyped sniffing have been observed after monoamine oxidase inhibitors

(nialamide and pargyline) given alone but only after larger or repeated doses (Randrup & Munkvad, 1966).

Biochemical analyses were made 5½ hr after pargyline. Each value (μg/g brain tissue) represents the mean ± the standard error of the mean of 5 experiments each performed on 3 pooled total brains.

The rats treated with DDC + pargyline show a significant decrease (Student's *t*-test) of the brain noradrenaline ($P < 0.001$) and normetanephrine ($P < 0.001$). The values were 0·085 ±0·01 and 0·039 ±0·002, respectively, compared with the rats receiving pargyline only: noradrenaline = 0·61 ±0·04 and normetanephrine = 0·086 ±0·007.

Furthermore, DDC seems to induce a slight increase in the level of dopamine ($P = 0.05$) and a significant increase of 3-*O*-methylated dopamine ($P < 0.001$). The values were 1·19 ±0·05 and 0·41 ±0·04, respectively, compared with the pargyline controls: dopamine = 0·97 ±0·09 and 3-methoxytyramine = 0·18 ±0·02.

For rats receiving DDC only, 4 times, the corresponding values for the brain amines are (3 analyses): noradrenaline = 0·054 ±0·01, normetanephrine <0·01, dopamine = 0·76 ±0:07 and 3-methoxytyramine = 0·035 ±0·003.

The production of aggressive behaviour by a pharmacological treatment which lowers brain noradrenaline was unexpected since other evidence indicates an association of aggressive behaviour with increased activity of brain noradrenaline (Gunne & Lewander, 1966; Scheel-Krüger & Randrup, 1967; Reis & Fuxe, 1968).

As a likely explanation for the above results the possibility exists that dopamine mimics the action of noradrenaline in central noradrenaline neurons. However, according to Carlsson, Fuxe & Hökfelt (1967), dopamine does not accumulate in central noradrenaline neurons, after treatment with DDC plus the monoamine oxidase inhibitor nialamide.

It is thus possible that features of aggressive behaviour are produced by disturbances of the balance between the aminergic systems in the brain. It is also possible that the aggressive behaviour observed is produced by some still unknown biochemical effect of DDC.

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Sct. Hans Hospital,
Department E,
Roskilde, Denmark.
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J. SCHEEL-KRÜGER
A. RANDRUP

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