Short communications

Effect of central catecholamine alterations on the hypothermic response to 6-hydroxydopamine in desipramine treated rats

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The hypothermia observed in rats kept in a cold environment after the intracisternal administration of 6-hydroxydopamine was enhanced by desipramine. Since pretreatment with 6-hydroxydopamine virtually eliminated the temperature fall in response to a subsequent dose of 6-hydroxydopamine, brain catecholamines were implicated in the response. Preferential reduction of brain noradrenaline antagonized the hypothermia after 6-hydroxydopamine in desipramine-treated rats to a greater extent than did the preferential reduction of dopamine. The results indicate the importance of noradrenergic fibres in this hypothermic response, but do not exclude an involvement of brain dopaminergic pathways.

After administration of 6-hydroxydopamine to the brain of rats, a fall in rectal temperature occurred whether it was given intraventricularly and the rats kept at room temperature (Simmonds & Uretsky, 1970) or intracisternally and the rats kept in the cold (Howard, Leahy & Breese, 1971). Since these responses were antagonized by treating animals several weeks before with 6-hydroxydopamine, the acute hypothermia to 6-hydroxydopamine was proposed to be due to endogenous release of catecholamines (Simmonds & Uretsky, 1970; Howard *et al.*, 1971). However, the individual importance of either noradrenaline or dopamine in this hypothermia does not appear to be clearly defined.

Simmonds & Uretsky (1970) reported that protriptyline, which antagonized the chronic depletion of noradrenaline by 6-hydroxydopamine without altering dopamine depletion (Evetts & Iversen, 1970), did not reduce the acute hypothermia produced by 6-hydroxydopamine at room temperature. Such data suggested that the hypothermia might be due to a release of brain dopamine. However, recent studies in our laboratory indicated that the hypothermic response to 6-hydroxydopamine was related to a noradrenergic mechanism (Howard *et al.*, 1971). Since we recently observed in the cold that protriptyline and desipramine did not block but potentiated the hypothermic response to 6-hydroxydopamine in rats kept at +3°C it was our purpose to determine what effect specific alteration of catecholamines would have on this response to 6-hydroxydopamine in desipramine-treated rats.

Methods.—6-Hydroxydopamine (150 μg in 25 μl 0·9% NaCl solution containing 0·5% ascorbic acid) was injected intracisternally in male Sprague-Dawley rats (170-190 g) under light ether anaesthesia. Saline containing 0·5% ascorbic acid was administered to control rats. Desipramine (25 mg/kg i.p.) was given 60 min before the administration of 6-hydroxydopamine. Rectal temperatures were recorded by a tele-thermometer from Yellow Springs Instrument Company. Thirty minutes after the intracisternal administration of 6-hydroxydopamine rats were placed into individual pre-chilled plastic cages kept at +3° C.

In some rats the brain concentrations of dopamine and noradrenaline were reduced (' central sympathectomy ') by pretreatment with two doses of 6-hydroxydopamine (200 μg), one dose 30 min after pargyline (50 mg/kg) and the second dose one week later without pargyline (Breese & Traylor, 1970; 1971). In other rats brain noradrenaline was preferentially depleted, with little effect on dopamine, by two injections of 25 μg 6-hydroxydopamine and one of 50 μg one week apart (Breese & Traylor, 1971). To reduce brain dopamine preferentially, 6-hydroxydopamine (200 μg) was administered 60 min after desipramine (Breese & Traylor, 1971). Animals were not used for at least two weeks after the last injection of 6-hydroxydopamine.

For measurement of brain concentrations of noradrenaline and dopamine, rats were killed by cervical fracture and decapitated. The brains were removed, rinsed, homogenized in 10 ml ice-cold 0·4 N perchloric acid and frozen. After thawing and centrifugation of the homogenate, an aliquot of the supernatant was analysed for catecholamines as previously described (Breese & Traylor, 1970).

Results.—Animals were pretreated with desipramine (25 mg/kg) 1 h before receiving 150 μg of 6-hydroxydopamine intracisternally. Thirty minutes after giving 6-hydroxydopamine the animals were placed in the cold. Within 90 min rectal temperatures had fallen to 26·1° ± 0·8° C (Fig. 1) which was significantly lower than the 32·5 ± 0·5° C observed at this time after 6-hydroxydopamine alone ($P<0.001$) (not plotted). It should be noted that desipramine alone also caused a mild hypothermia ($P<0.01$).

To establish that the response to 6-hydroxydopamine in desipramine-treated rats was related to release from endogenous catecholamine stores, animals were 'centrally sympathectomized' (see **Methods**) with 6-hydroxydopamine so that both dopamine and norepinephrine would be reduced. After this treatment, the hypothermia to intracisternally administered 6-hydroxydopamine in desipramine-treated animals was virtually absent (Fig. 1). Preferential reduction of noradrenaline also prevented the reduction in rectal tempera-

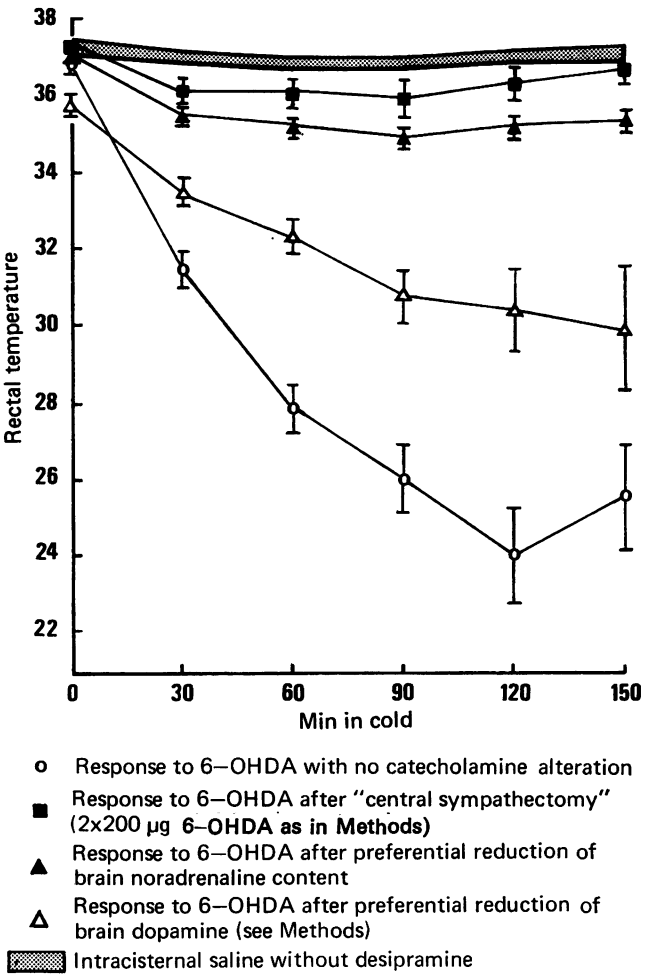

FIG. 1. Effect of brain catecholamine content on the fall in rectal temperature of rats following an intracisternal injection of 6-hydroxydopamine (6-OHDA) to desipramine-treated rats. All groups except the control group received desipramine (25 mg/kg, i.p.) prior to 6-OHDA (150 μg). Control animals received vehicle intracisternally. Rats were placed in the cold (+3° C) 30 min after the intracisternal injection of 6-OHDA or vehicle. Note that the response to saline in desipramine-treated rats is not significantly different from the response to 6-OHDA after preferential reduction of brain noradrenaline. Each point is the mean ± S.E. of at least 6 rats.

ture in response to 6-hydroxydopamine. Preferential reduction of brain dopamine also antagonized the hypothermic response to 6-hydroxydopamine but to a lesser degree than preferential reduction of noradrenaline (Fig. 1).

The finding that the release of noradrenaline was apparently more important to the hypothermia in response to 6-hydroxydopamine in desipramine-treated animals than dopamine was difficult to reconcile with the finding that desipramine antagonized the long-term effects of 6-hydroxydopamine on noradrenergic fibres (Breese & Traylor, 1971). Examination of the catecholamine concentrations in the brain 1 h and 5 days after administering 6-hydroxydopamine to animals that had previously received desipramine seemed necessary to clarify this observation. One hour after intracisternally administered 6-hydroxydopamine (150 μg) the brain noradrenaline concentration fell from $0{\cdot}58 \pm 0{\cdot}02$ μg/brain to $0{\cdot}25 \pm 0{\cdot}01$ μg/brain in rats treated with desipramine compared with a reduction to $0{\cdot}10 \pm 0{\cdot}01$ μg/brain in rats which did not receive desipramine. The dopamine concentrations were not reduced at this time. After 5 days, the brain noradrenaline concentration was $0{\cdot}51 \pm 0{\cdot}04$ μg/brain in the animals pretreated with desipamine and $0{\cdot}22 \pm 0{\cdot}01$ μg/brain in the untreated animals. These latter values clearly indicate the protection which desipramine treatment affords noradrenaline-containing fibres to the long-term destructive effects of 6-hydroxydopamine. They are in contrast to the noradrenaline depletion observed at 1 hour. Five days after the 6-hydroxydopamine injection the brain dopamine concentration had fallen from $0{\cdot}90 \pm 0{\cdot}03$ μg/brain to $0{\cdot}40 \pm 0{\cdot}02$ μg/brain in desipramine-pretreated rats and to $0{\cdot}35 \pm 0{\cdot}03$ μg/brain in untreated rats. This indicates that desipramine does not influence the chronic effect of 6-hydroxydopamine on dopaminergic fibres.

Discussion.—Simmonds & Uretsky (1970) found recently that pretreatment with protriptyline before administering 6-hydroxydopamine did not reduce the hypothermia caused by an intraventricular injection of 6-hydroxydopamine when the rats were kept at room temperature. In the present study it was observed that in a cold environment desipramine not only did not reduce the hypothermic response to an intracisternal injection of 6-hydroxydopamine but potentiated it (Fig. 1). An explanation for the enhanced hypothermic response to 6-hydroxydopamine after desipramine probably encompasses an inhibition of uptake of brain catecholamines by desipramine after being released by 6-hydroxydopamine (Axelrod, Whitby & Hertting, 1961), but a peripheral effect of desipramine cannot be discounted.

The absence of the hypothermic response to 6-hydroxydopamine in desipramine-treated rats after 'central sympathectomy' adds further evidence to the view that the hypothermia produced by 6-hydroxydopamine is related to the release of endogenous stores of catecholamines (Fig. 1). In an attempt to take a more specific approach and to evaluate the role of a given catecholamine in the hypothermic response to 6-hydroxydopamine, the brain noradrenaline content was preferentially reduced. It was found that this treatment virtually eliminated the hypothermia. While this finding would be unexpected in view of the report that protriptyline did not alter the hypothermia to inventricularly injected 6-hydroxydopamine at room temperature (Simmonds & Uretsky, 1970), it is compatible with our previous finding that noradrenaline alone was responsible for the hypothermia to intracisternally administered 6-hydroxydopamine in the cold (Howard *et al.*, 1971). It should be pointed out that the temperature at which the studies were run as well as the routes of administration were different and could account for these apparent discrepancies.

Evidence supporting the view that dopamine may be involved in temperature control is scant. The injection of dopamine into the brain was reported to produce a slight rise in body temperature (Myers & Yaksh, 1968). On the other hand, apomorphine, a compound suggested to stimulate dopaminergic receptors, decreases body temperature (Fuxe, Hökfelt & Ungerstedt, 1970). In the present study, preferential reduction of dopamine significantly decreased the hypothermia after 6-hydroxydopamine in the desipramine-treated rats, although not to the extent that preferential reduction of noradrenaline did. This suggests the possibility of the participation of a dopaminergic pathway. However, a slight noradrenaline decrease accompanies the preferential reduction of dopamine and may conceivably be related to the fibres involved in the hypothermic response of 6-hydroxydopamine. Further examination of the

problem will be required to resolve this uncertainty and the role of dopamine in temperature control mechanisms.

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