J. Pharm. Pharmac., 1968, **20**, 204–209 Received September 13, 1967

Peripheral and central components in the hyperthermic effect of desipramine in reserpinized rats

D. BERNARDI, S. PAGLIALUNGA AND A. JORI

Pithed rats show a decrease of body temperature which is not affected by reserpine, cocaine or desipramine. Noradrenaline decreases the rate of fall of body temperature and this effect is enhanced by pretreatment with cocaine or desipramine. Reserpine with desipramine or with cocaine also produces a decreased rate of fall of body temperature. But if reserpine is given 18 hr before pithing, desipramine is without effect although noradrenaline and 2,4-dinitrophenol produce a calorigenic response. The hyperthermic effect of desipramine in reserpinized rats is also decreased by spinal transection. Lumbar transection is less effective than cervical transection. It is concluded that the integrity of the central nervous system is required for the development of the hyperthermic effect of desipramine in previously reserpinized rats.

THE possible mechanisms of the interaction between reserpine and tricyclic antidepressant drugs, such as desipramine, on the body temperature of rats have been summarized by Garattini & Jori (1967). It has been established that when imipramine-like drugs are given before reserpine, they enhance and prolong the hyperthermic phase and prevent the succeeding hypothermia (Garattini, Giachetti & others, 1962; Jori, Paglialunga & Garattini, 1967), but when they are given to hypothermic reserpinized rats they induce an increase of body temperature (Askew, 1963; Jori & Garattini, 1965).

The temperature increase is still evident when desipramine is injected directly into the brain of fully reserpinized rats (Bernardi, Jori & others, 1966; Reverski & Jori, 1968).

We now present evidence that the integrity of the central nervous system (CNS) is a necessary condition for the onset of the desipramine effect on body temperature of reserpinized rats.

Experimental

Female Sprague Dawley rats, 150–180 g, were used. Some animals were pithed under a light ether anesthesia with a needle introduced into the orbital cavity, the needle was also used to destroy the spinal cord. In other animals, spinal transections were made under ether anaesthesia at a cervical, thoracic or lumbar level. Tracheotomy and artificial ventilation were performed immediately after destruction of the CNS or after the cervical transection. After the operation, a thermistor was inserted into the rectal cavity and the body temperature continuously recorded by an automatic device (Jori & Paglialunga, 1966).

In general, the experiments were made at 22° and a relative humidity of 60%. Some animals were kept at 35° to avoid marked fall of body temperature. Drugs were injected in pithed rats, when the body temperature reached 35° ± 1°.

Drugs administered after spinal transection were generally given intravenously, to eliminate the possibility of an impaired absorption.

From the Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea, 62-20157 Milan, Italy.

The drugs used were: noradrenaline bitartrate (Recordati), 2,4-dinitrophenol (C. Erba), reserpine (Serpasil, CIBA), desipramine (Pertrophan, Geigy), (+)-amphetamine sulphate (Recordati), cocaine hydrochloride (C. Erba).

Results

Effect of desipramine and other agents on the body temperature of pithed rats. The pithed rats were unable to regulate body temperature by any central mechanism and immediately after destruction of the CNS there was a fall in rectal temperature (Fig. 1A). The rate of fall depended on the environmental temperature and also on the initial body temperature of the rat. Consequently the drugs were administered to pithed rats when the rectal temperature was 35° ± 1°. Noradrenaline, infused for 15 min

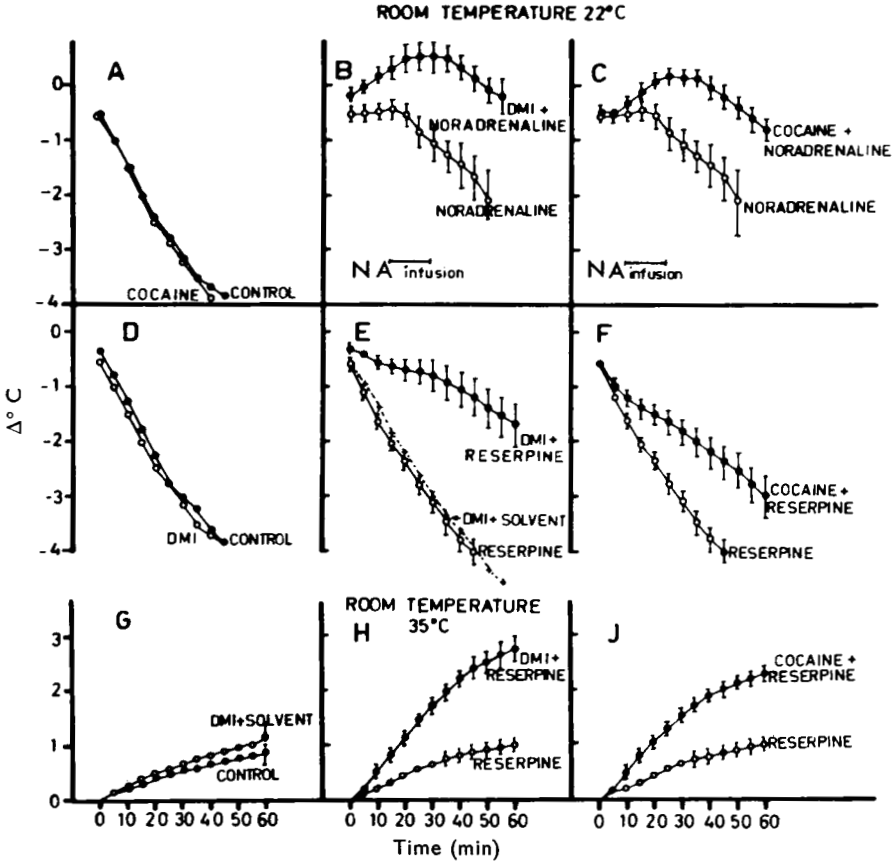

FIG. 1. Changes of body temperature in pithed rats given intravenously saline (control) or reserpine solvent (solvent), or reserpine (2·5 mg/kg) or noradrenaline (infused for 15 min at a rate of 0·1 ml/min at a concentration of 40 μl/ml). Cocaine (5 mg/kg i.v.) or desipramine (15 mg/kg i.p.) were given 5 min and 1 hr respectively before pithing.

at a rate of 0·1 ml/min (40 μg/ml), 5 min after the operation delayed the onset of the hypothermia (Fig. 1B).

Pretreatment with desipramine (15 mg/kg, i.p.) or cocaine (5 mg/kg, i.v.) much increased the noradrenaline effect (Fig. 1B and C) but the drugs themselves had no effect (Fig. 1A, D and E). Fig. 1E shows also that reserpine (2·5 mg/kg, i.v.) given at the time of pithing did not modify the fall of the body temperature. But when desipramine was given 1 hr before pithing, the reserpine injection significantly reduced the rate and the intensity of the fall of body temperature (Fig. 1E). The same results, although less marked, were obtained in animals pretreated with cocaine (Fig. 1F).

A hyperthermic effect was also present when cocaine or desipramine was given before reserpine and pithing to rats maintained at 35° (Fig. 1G, H, J).

Effect of desipramine and other drugs on body temperature of reserpinized pithed rats. Fig. 2 shows the effect of desipramine in normal and pithed

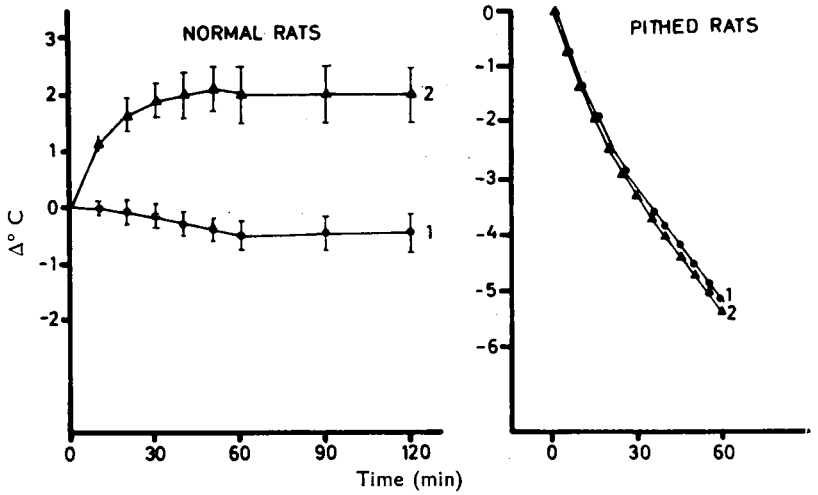

FIG. 2. Changes of body temperature induced by desipramine (1·5 mg/kg, i.v.) (curve 2) or by saline (curve 1) in rats treated 18 hr before with reserpine (2·5 mg/kg, i.v.).

rats given reserpine 18 hr previously. Desipramine produced a rapid hyperthermic effect in intact rats but no activity was apparent when the drug was injected immediately after pithing. The same results were obtained when the experiment was at 35°.

Other hyperthermic agents were given to previously reserpinized rats about 5 min after they were pitted (Table 1). Amphetamine was inactive was given before reserpine and pithing to rats maintained at 35° (Fig. but noradrenaline and dinitrophenol significantly reduced the fall in body temperature.

Effect of spinal transections. Animals were pretreated with reserpine 18 hr before spinal transection. Fig. 3 shows that the hyperthermic effect induced by desipramine progressively decreased when transections were made at the lumbar (L_4), thoracic (T_2–T_3) and cervical (C_2–C_3) level.

TABLE 1. EFFECT OF HYPERTHERMIC AGENTS ON BODY TEMPERATURE OF PITHED RATS PREVIOUSLY RESERPINIZED

No. of rats	Treatment mg/kg i.v.		Body temp decrease. after 60 min (°C) ± s.e.
12	Controls		6·1 ± 0·2
6	2,4-Dinitrophenol	7·5	4·1 ± 0·1 ($P<0·01$)
6	Noradrenaline	0·24	4·0 ± 0·2 ($P<0·01$)
4	Amphetamine	7·5	5·9 ± 0·2

Reserpine (2·5 mg/kg, i.v.) was given 18 hr before pithing. Hyperthermic agents were given about 5 min after the operation. Noradrenaline (40 μg/ml, was infused at the rate of 0·1 ml/min for 15 min.

Discussion

Pithed rats, artificially respired, lost heat at an almost constant rate of about 1°/10 min when the room temperature was 22°. In these animals reserpine given immediately after pithing or 18 hr earlier did not significantly modify the onset of the hypothermia.

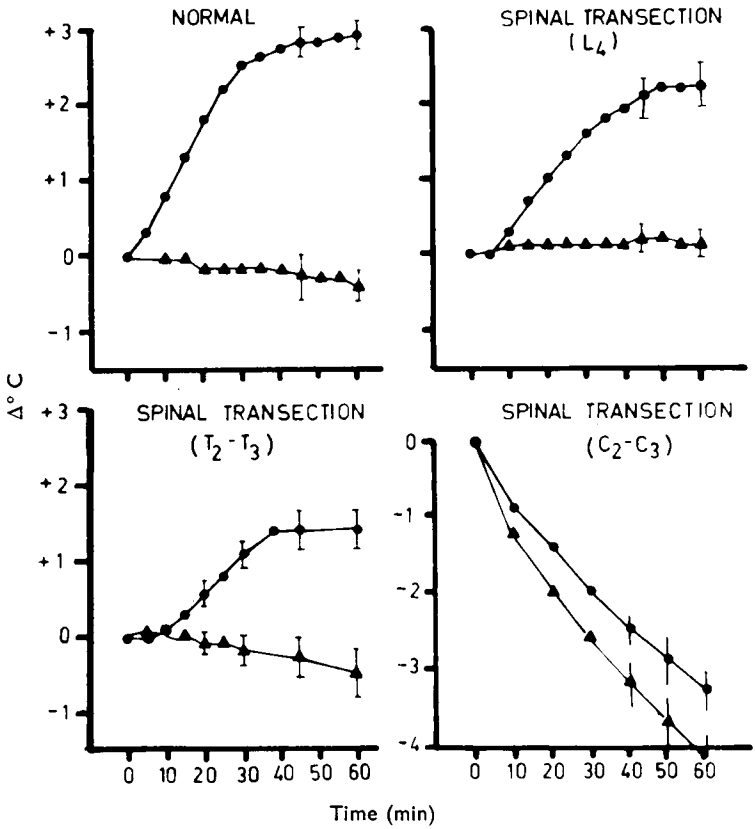

FIG. 3. Changes of body temperature induced by desipramine (—●—) (15 mg/kg, i.v.) or saline (—▲—) in rats treated 18 hr before with reserpine (2·5 mg/kg, i.v.). Spinal transection was performed 15 min before giving desipramine.

Reserpine injected intravenously into normal rats at the same dose is known to elicit a marked hyperthermia probably related to the release of central and peripheral catecholamines (Jori & others, 1967).

The difference in response to reserpine of pithed and normal rats is not due to the pithed animals losing body heat because at an ambient temperature of 35°, the pithed rats were in a phase of a slow increase of body temperature, but reserpine was still ineffective (Fig. 1). Further, pithed rats were still sensitive to the calorigenic action of noradrenaline as shown by the inhibition of the hypothermia after infusion with this amine (Fig. 1).

Reserpine is still able to release catecholamines in spinalized rats although its effect is more marked on the nerve terminals cranial than caudal to the lesion (Anden, Fuxe & Hökfelt, 1966, 1967). Probably the amount or the rate at which catecholamines are released by reserpine in pithed rats is not enough to counteract the loss of body temperature.

As expected, the calorigenic effect of noradrenaline in pithed rats is potentiated in the same way as it is in normal rats (Jori & others, 1967), by drugs such as desipramine and cocaine which inhibit catecholamine uptake (Glowinski & Axelrod, 1964; Iversen, 1965; Hillarp & Malmfors, 1964). Desipramine and cocaine, although they do not themselves affect the fall of body temperature in pithed rats, make a pre-operative injection of reserpine calorigenic. This effect is also present at 35° (Fig. 1). Desipramine given before reserpine, potentiates and prolongs the hyperthermic phase which follows reserpine (Jori & others, 1967). These results may be interpreted assuming that the catecholamines released by reserpine in pithed rats become calorigenic if the inhibition of their uptake makes them more available at the receptor sites (Garattini & Jori, 1967). Further, desipramine slows the rate at which reserpine releases catecholamines (Manara, Sestini & others, 1966; Manara, Algeri & Sestini, 1967).

A different situation is present when desipramine is given to fully reserpinized hypothermic rats (reserpine was usually given 18 hr before the experiment). While in normal animals desipramine increases body temperature, this effect is abolished if the animals are pithed before receiving desipramine.

Reserpinized pithed rats do not respond to the hyperthermic effect of amphetamine, presumably of central origin, although they are still sensitive to the calorigenic action of noradrenaline infusion and to a peripheral hyperthermic agent such as 2,4-dinitrophenol (Buffa, Carafoli & Muscatello, 1963) (see Table 1). It therefore seems logical to conclude that the hyperthermic response of desipramine in previously reserpinized rats is of central origin.

In an attempt to localize the site of action of desipramine several spinal transections were made. The hyperthermic effect of this agent in reserpinized rats tends to reappear the more caudal the lesion.

Thus it seems that desipramine is acting at a high level in the central nervous system and that the pathways carrying the stimulation to the periphery pass through the spinal cord.

Acknowledgement. The technical assistance of Mr. L. Guarnieri is gratefully acknowledged.

References

Anden, N. E., Fuxe, F. & Hökfelt, T. (1966). *J. Pharm. Pharmac.*, **18**, 630–632.
Anden, N. E., Fuxe, F. & Hökfelt, T. (1967). *European J. Pharmac.*, **1**, 226–232.
Askew, B. M. (1963). *Life Sci.*, **10**, 725–730.
Bernardi, D., Jori, A., Morselli, P., Valzelli, L. & Garattini, S. (1966). *J. Pharm. Pharmac.*, **18**, 278–282.
Buffa, P., Carafoli, E. & Muscatello, V. (1963). *Biochem. Pharmac.*, **12**, 769–778.
Garattini, S., Giachetti, A., Jori, A., Pieri, L. & Re, R. (1962). *J. Pharm. Pharmac.*, **14**, 509–514.
Garattini, S. & Jori, A. (1967). In *First Intern. Symposium on Antidepressant Drugs.* Editors Garattini, S. & Dukes, M. N. G. Amsterdam: Excerpta Medica Foundation, Congress Series n. 122, pp. 179–193.
Glowinski, J. & Axelrod, J. (1964). *Nature, Lond.*, **204**, 1318–1319.
Hillarp, N. H. & Malmfors, T. (1964). *Life Sci.*, **3**, 703–708.
Iversen, L. L. (1965). *J. Pharm. Pharmac.*, **17**, 62–64.
Jori, A. & Garattini, S. (1965). *Ibid.*, **17**, 480–488.
Jori, A. & Paglialunga, S. (1966). *Medna Pharmac. Exp.*, **14**, 513–514.
Jori, A., Paglialunga, S. & Garattini, S. (1967). *Archs int. Pharmacodyn. Thér.*, **165**, 384–393.
Manara, L., Algeri, S. & Sestini, M. G. (1967). In *First Intern. Symposium on Antidepressant Drugs.* Editors Garattini, S. & Dukes, M. N. G. Amsterdam: Excerpta Medica Foundation, Congress Series n. 122, pp. 51–60.
Manara, L., Sestini, M. G., Algeri, S. & Garattini, S. (1966). *J. Pharm. Pharmac.*, **18**, 194–195.
Reverski, W. & Jori, A. (1968). *Ibid.*, **20**, in the press.