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# Can Haloperidol Disguise Fever ?

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## Summary

Haloperidol when applied intraperitoneally to cold-exposed febrile rabbits induces a strong hypothermic effect. This effect is due to the downward shift of the threshold central temperature for induction of cold thermogenesis and vasomotion. The shift occurs during the early phase of the fever and is less prominent during the late phase of the fever. The hypothermic effect of high doses of haloperidol can eliminate the increase of body temperature in febrile individuals.

**Key words**

Fever – Haloperidol – Thermoregulatory thresholds

## Introduction

Haloperidol, a dopamine antagonist, is being extensively used as a neuroleptic substance. Interacting with D2 receptors it has also a central depressive effect on thermoregulation in warm- as well as cold-exposed subjects (for review see Clark and Lipton 1991). In normothermic rabbits intraperitoneal injections of haloperidol induce a striking shift of the threshold temperature for induction of thermoregulatory outputs to lower body temperature, without influencing their intensity and hypothalamic thermosensitivity. Intrahypothalamic injections of haloperidol are without effect or induce mild hyperthermia, due to depression of panting and peripheral vasomotor tone (Vybíral and Janský 1989).

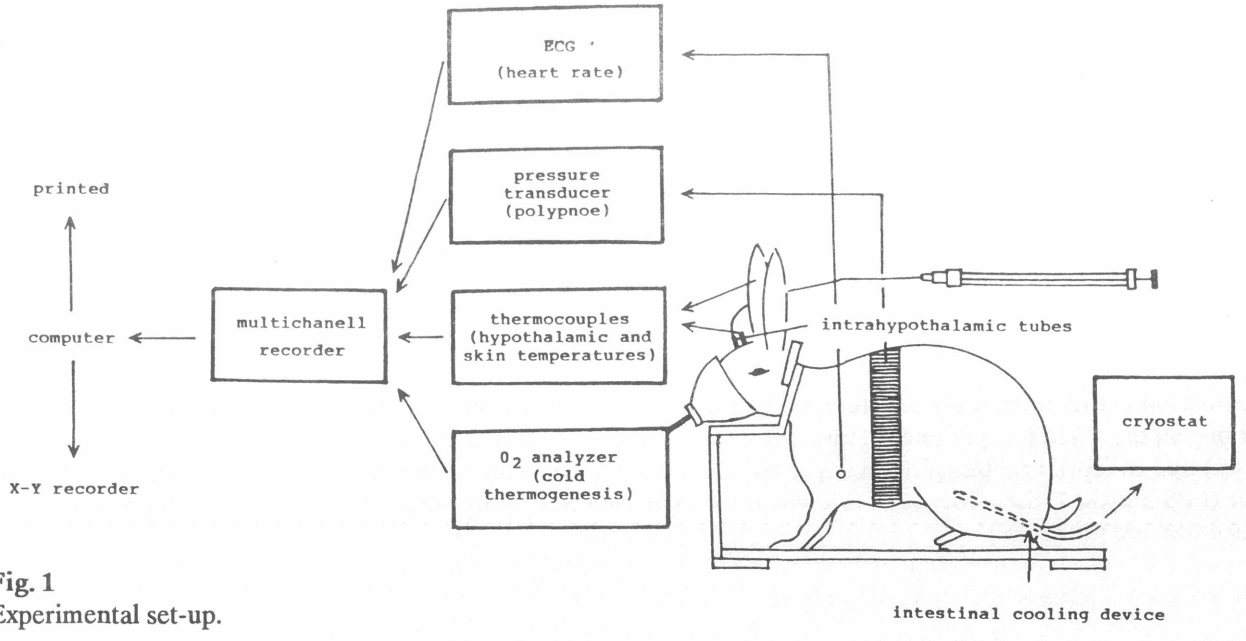


**Fig. 1**
Experimental set-up.

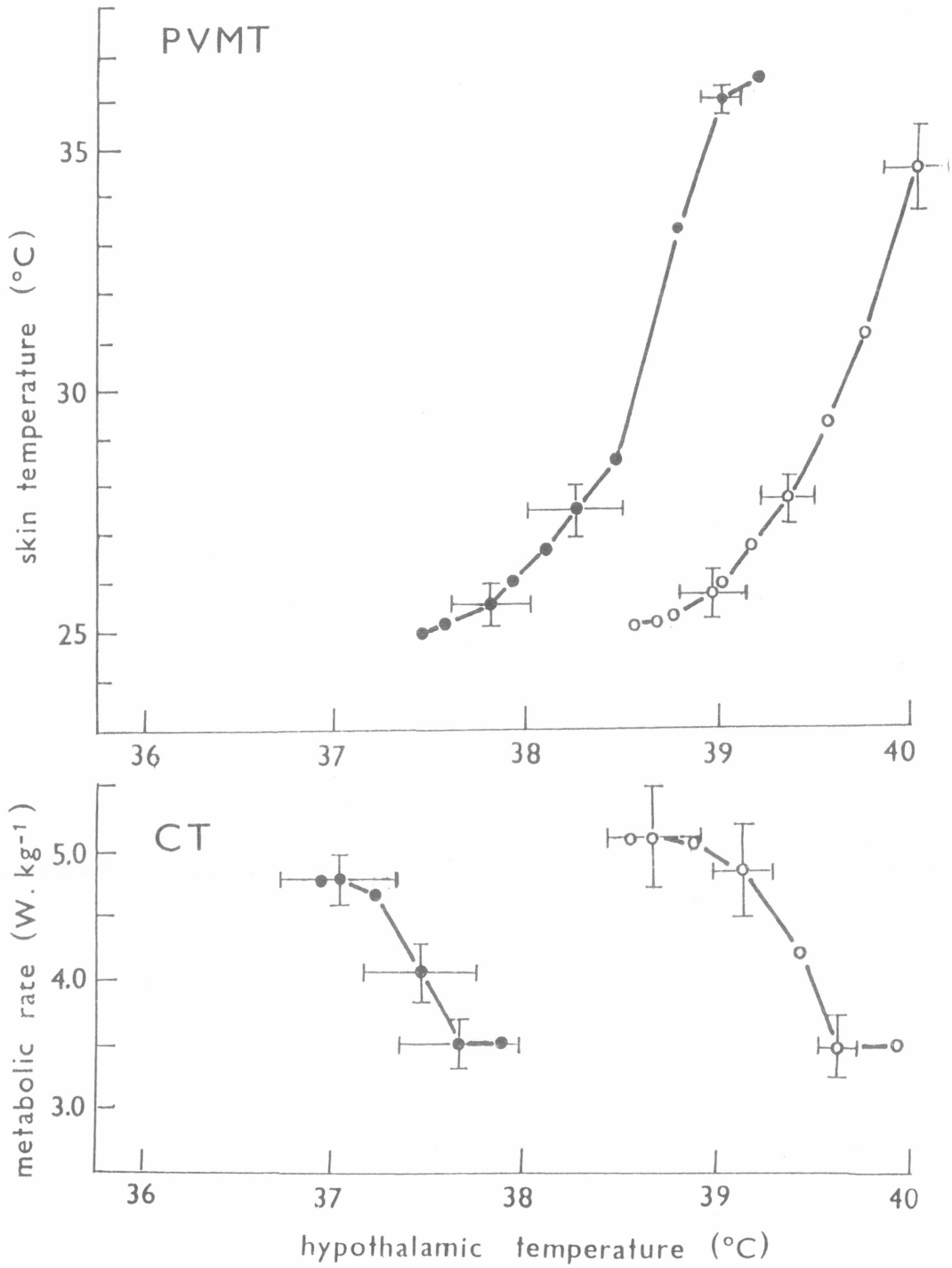


**Fig. 2**
Relationship between the body core temperature and intensity of individual thermoregulatory effectors (CT - cold thermogenesis, PVMT - peripheral vasomotor tone) during intestinal cooling in control febrile rabbits (open circles) and in febrile rabbits given haloperidol (2.5 $mg.kg^{-1}$ i.p.) (closed circles) in the early phase of endotoxin fever (LPS 5 $\mu g.kg^{-1}$ i.v.). Means ± S.E.M from 6 experiments. (Control data for endotoxin and for endotoxin + haloperidol are not given.)

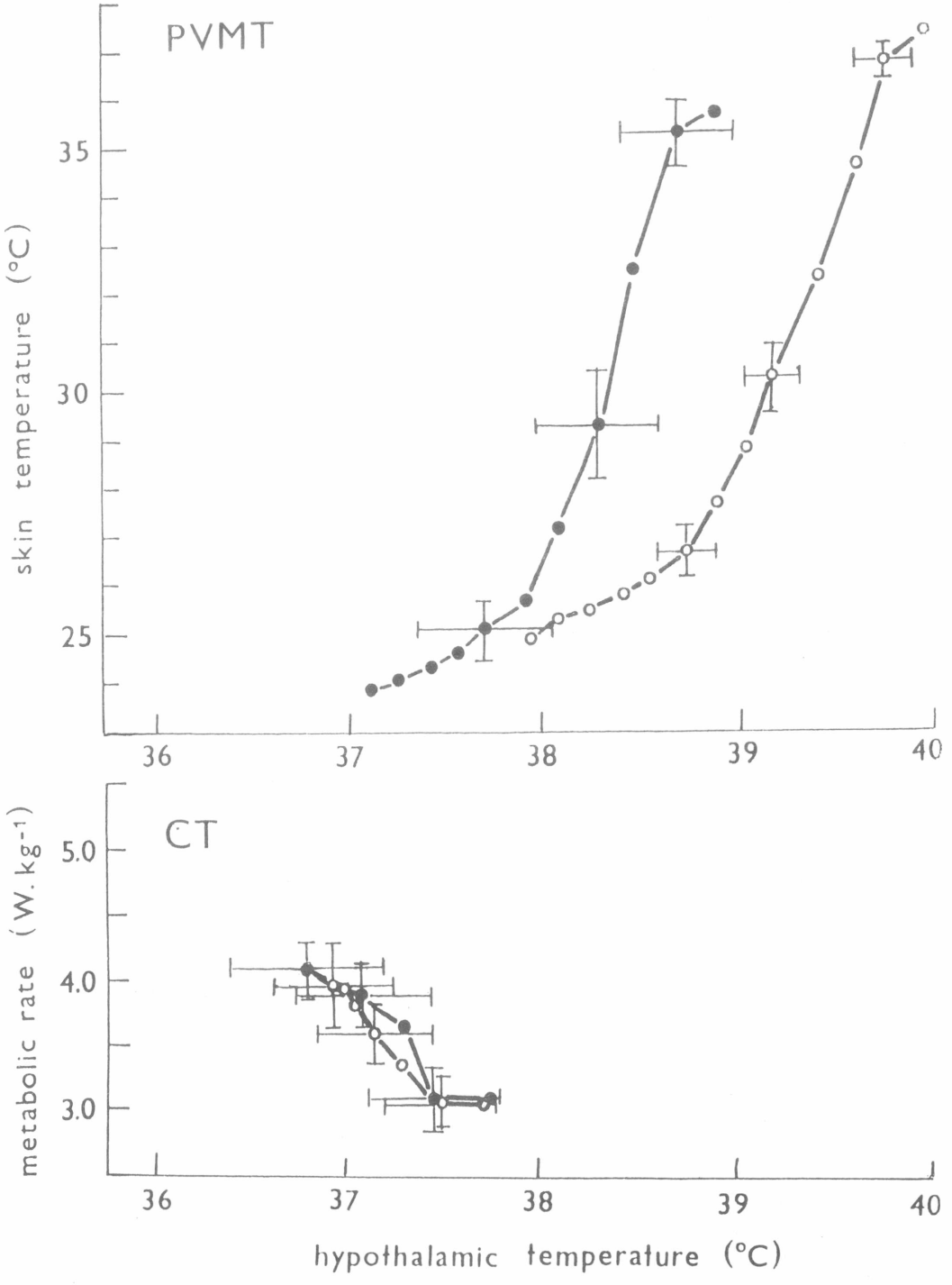


**Fig. 3**
Relationship between the body core temperature and intensity of individual thermoregulatory effectors (CT - cold thermogenesis, PVMT - peripheral vasomotor tone) during intestinal cooling in control febrile rabbits (open circles) and in febrile rabbits given haloperidol (2.5 $mg.kg^{-1}$ i.p.) (closed circles) in the late phase of endotoxin fever (LPS 5 $\mu g.kg^{-1}$ i.v.). For other details see Fig. 2.

Two phases of the thermoregulatory response can be distinguished in the course of fever (Vybíral *et al.* 1987, Iriki *et al.* 1984, Hashimoto *et al.* 1985). During the early phase of the fever, occurring within the first 100 min, the increase in body temperature is due to the shift of threshold body temperature for inducing of cold thermogenesis, panting and release of the peripheral vasomotor tone to higher body temperatures. The late phase of the fever is characterized by a downward shift of the threshold body temperature for shivering, while that for vasomotion remains elevated, so that a dissociation of thresholds for cold and warm defence mechanisms occurs. The capacity of cold thermogenesis during the endotoxin fever is reduced.

The effect of intraperitoneal injections of haloperidol on thermoregulation in the early and/or late phase of fever has not yet been studied and the mode of haloperidol action on thermoregulatory centres has not been elucidated.

## Methods

Thermoregulatory functions of rabbits were analysed by means of the method of intestinal cooling (Inomoto *et al.* 1982) (Fig. 1). This method enables the manipulation of central body temperature while leaving the peripheral body temperature relatively unaffected. The values of cold thermogenesis (CT – measured as oxygen consumption) and peripheral vasomotor tone (PVMT – ear skin temperature) were monitored at 3 min intervals, first in normal rabbits (receiving an injection of pyrogen-free saline) during intestinal cooling till cold thermogenesis is fully activated. After rewarming of animals, the tested substances (lipopolysaccharide – LPS and haloperidol) were injected and intestinal cooling was repeated. Values of oxygen consumption and skin temperature were then expressed as functions of central body temperature measured in the hypothalamus. On the basis of these data it was possible to determine the capacity and the threshold temperature for induction of individual thermoregulatory effectors (CT, PVMT) as well as the thermosensitivity of hypothalamic control centers. Further methodical details are given in the paper of Vybíral *et al.* (1986). Haloperidol was administered intraperitoneally in a dose 2.5 $mg.kg^{-1}$ to rabbits made febrile by the intravenous injection of lipopolysaccharide (*S. typhosa* 5 $\mu g \cdot kg^{-1}$). Haloperidol was injected immediately after injection of LPS or 120 min later, i.e. in the early or in the late phase of the fever. In both cases intestinal cooling was started 18 min after administration of haloperidol.

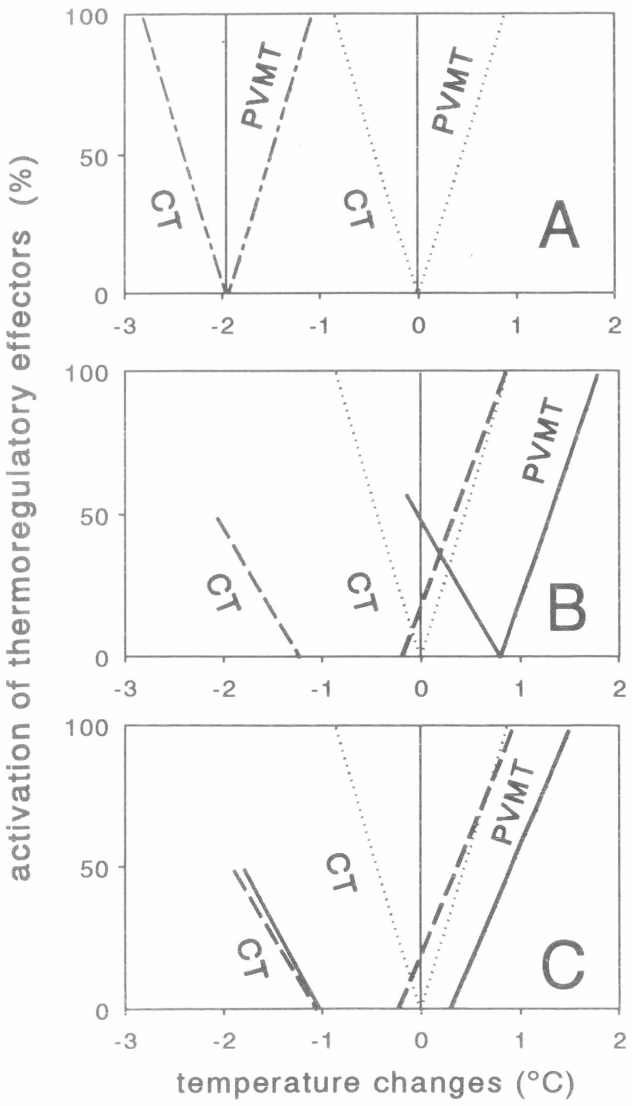


**Fig. 4**
Scheme of activation of individual thermoregulatory effectors (CT, PVMT) due to changes in central body temperature in control rabbits (dotted line), after haloperidol (2.5 $mg.kg^{-1}$ i.p.) (dashed line) (panel A) as well as in control febrile rabbits (*S. typhosa* 5 $\mu g.kg^{-1}$ i.v.) (full line) and in febrile rabbits given haloperidol (broken line) in the early (panel B) or the late (panel C) phases of the fever.

## Results and Discussion

Intraperitoneal injections of haloperidol in the early phase of the fever induce a hypothermic effect due to a shift of the thresholds for cold thermogenesis and peripheral vasomotor tone to lower body temperatures (Fig. 2 and 4B). The shift of the threshold body temperature for shivering is more prominent than that for vasomotion, the consequence being an enlargement of the interthreshold zone when thermoregulation is not activated. The earlier results

observed in normothermic rabbits given haloperidol (Fig. 4A) (Vybíral and Janský 1989) indicate that the hypothermic effect of this substance in the early phase of the fever found in this study is connected with the febrile process.

The effect of the same dose of the i.p. applied haloperidol in the late phase of the fever does not influence the already lowered threshold for cold thermogenesis (Fig. 3 and 4C). The threshold for induction of the peripheral vasomotor tone is slightly lowered, however, so that the interthreshold zone becomes narrower. Thus the haloperidol effect in the late phase of the fever is similar to that of ACTH, AVP and other natural antipyretic substances (Vybíral *et al.* 1988, Ehymayed and Janský 1992). Though it is generally accepted that the peripherally injected haloperidol penetrates into the brain, our previous experiments (Vybíral and Janský 1989) indicate that intrahypothalamically injected haloperidol has rather a hyperthermic effect. The reason for this discrepancy remains unclear.

Our data indicate that heavy doses of haloperidol when applied to febrile subjects can obscure fever.

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**Reprint requests**

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