Haloperidol produces hypothermic effects in rats[1]

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Summary. Intraperitoneal administration of either haloperidol or chlorpromazine produced hypothermia both in the cold (8 °C) and at room temperature (22 °C). The hypothermia was brought about both by a decrease in metabolic heat production and an increase in the cutaneous temperature of tail and foot skin. However, at a higher temperature (29 °C), there were no changes in rectal temperature and other thermoregulatory responses.

Several recent studies reported that chlorpromazine, a phenothiazine, produced a fall in rectal temperature in many species of animals by acting on the central nervous system[2-4]. Haloperidol, a butyrophenone, although structurally different from chlorpromazine, shares many of its pharmacological properties. However, it is not known whether haloperidol shares with chlorpromazine the ability to produce hypothermia. In the present study, therefore, the effects of systemic administration of both haloperidol and chlorpromazine on the thermoregulatory responses of unanesthetized rats to different ambient temperatures (T_a) of 8, 22 and 29 °C were assessed.

Materials and methods. Adult male Sprague-Dawley rats weighing between 250 and 300 g were used in all experiments. Measurements were obtained from conscious animals which were trained to sit quietly under minimal restraint in rat stocks[5]. Between experiments the animals were housed individually in wire-mesh cages in a room maintained at an ambient temperature of 25 ± 1.0 °C with a 12/12 h light-dark cycle. The animals were given free access to tap water and granular chicken feed. All drug solutions were prepared in pyrogen free glassware which was baked at 180 °C for 5 h before use. Haloperidol (McNeil Laboratories, Inc., Fort Washington, Pa., 1-5 mg/kg, i.p.) was freshly prepared in 0.9% saline with 0.5% tartaric acid. Chlorpromazine (Smith, Kline and French, 5-15 mg/kg, i.p.) was freshly prepared in 0.9% saline. For i.p. injection, drugs with doses expressed as mg of free base per kg of body weight, were administered i.p. in a volume of 1 ml/kg b.wt. Metabolic rate, respiratory evaporative heat loss and vasomotor activity were measured in a small partitional calorimeter. Metabolic rate (M) was calculated from the animal's oxygen consumption. Metabolic rate was calculated in W assuming an RQ = 0.83 so that 1 l of oxygen consumed per h was equivalent to a heat production of 5.6 W[6-8]. Respiratory evaporative heat loss (E_{res}) was calculated by measuring the increase in water vapor content in the helmet effluent air over that of the ambient air. Evaporative heat loss expressed as W was calculated from evaporative water loss assuming the latent heat of the evaporation of water to be 0.7 $W/h \cdot g^{-1}$[9]. Rectal (T_r), foot skin (T_f) and tail skin (T_t) temperatures were measured using copper-constantan thermocouples. Rectal temperature was measured with a copper-constantan thermocouple enclosed in PE 200 tubing, sealed at 1 end, inserted 6 cm into the rectum. Measurements were obtained every minute as a d.c. potentials with a Hewlett-Packard digital voltmeter (DVM 3455) interfaced online to a CPU 9825 computer which calculated temperatures, M and E_{res} and relayed them on an on-line HP printer 9871. Animals were kept for a period of 90 min at each ambient temperature to attain thermal balance before drug injection. The maximal changes in rectal temperature, foot skin temperature, tail skin temperature, metabolic rate and respiratory evaporative heatloss produced within 120-min period after drug injections were expressed as ΔT_r, ΔT_f, ΔT_t, ΔM and ΔE_{res}, respectively.

Results and discussion. The table shows that i.p. administration of either haloperidol or chlorpromazine produced a fall in rectal temperature both in the cold (8 °C T_a) and at room temperature (22 °C T_a). The hypothermia in response to haloperidol or chlorpromazine was brought about both by a decrease in metabolic heat production and an increase in cutaneous temperature of the tail and the footsole (figures 1 and 2). There was no change in E_{res}. However, at a higher temperature (29 °C T_a), there were no changes in

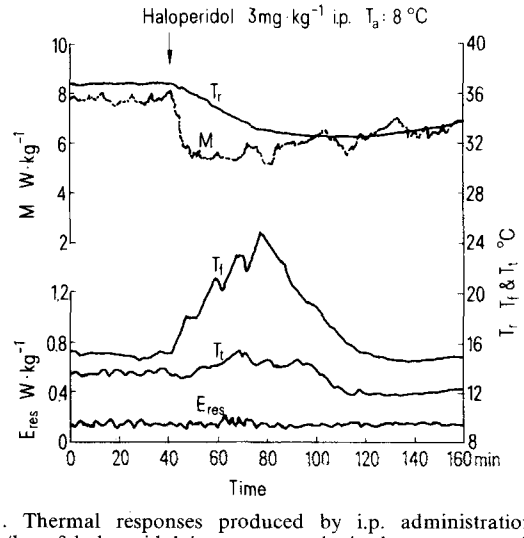

Fig. 1. Thermal responses produced by i.p. administration of 3 mg/kg of haloperidol in an unanesthetized rat at an ambient temperature (T_a) of 8 °C. T_r: rectal temperature; M: metabolic rate; T_f: foot skin temperature; T_t: tail skin temperature; E_{res}: respiratory evaporative heat loss.

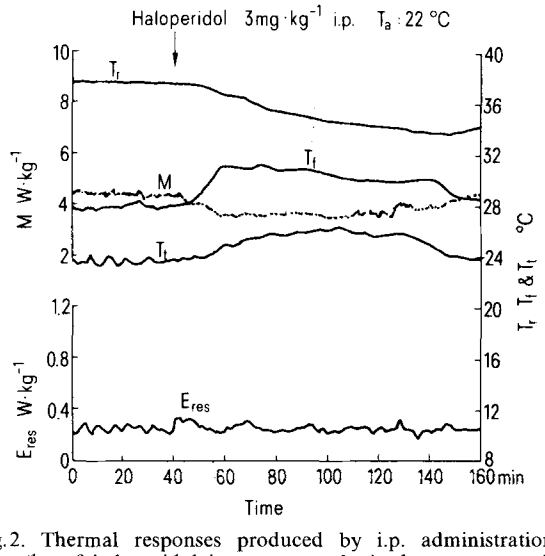

Fig. 2. Thermal responses produced by i.p. administration of 3 mg/kg of haloperidol in an unanesthetized rat at an ambient temperature (T_a) of 22 °C. T_r: rectal temperature; M: metabolic rate; T_f: foot skin temperature; T_t: tail skin temperature; E_{res}: respiratory evaporative heat loss.

The thermal responses produced by an injection of either haloperidol or chlorpromazine into the peritoneal cavity of conscious rats at 2 different ambient temperatures (T_a) of 8 and 22 °C. The maximal changes in rectal temperature, tail skin temperature, foot skin temperature, metabolic rate and respiratory evaporative heat loss produced within 120-min period after the injections were expressed as ΔT_r, ΔT_t, ΔT_f, ΔM and ΔE_{res}, respectively

Treatment of animals	No. of animals	T_a, °C	ΔT_r, °C	ΔT_t, °C	ΔT_f, °C	ΔM, W/kg	ΔE_{res}, W/kg
Vehicle control (i.p.)	4	8	0.2±0.13	0.4±0.15	0.5±0.21	0.2±0.08	0.03±0.02
Haloperidol 3 mg/kg (i.p.)	8	8	−4.0±0.27*	−1.2±0.32**	7.4±0.96**	−2.1±0.24**	0.02±0.02
Chlorpromazine 10 mg/kg (i.p.)	8	8	−4.6±0.31*	2.1±0.63**	6.2±0.84**	−2.6±0.27**	0.04±0.03
Vehicle control (i.p.)	4	22	0.2±0.11	0.6±0.24	0.7±0.36	0.3±0.09	0.03±0.02
Haloperidol 1 mg/kg (i.p.)	4	22	−2.1±0.18*				
Haloperidol 3 mg/kg (i.p.)	8	22	−3.1±0.19*	2.0±0.46**	2.8±0.52**	−1.0±0.15**	0.03±0.02
Haloperidol 5 mg/kg (i.p.)	4	22	−4.0±0.21*				
Chlorpromazine 5 mg/kg (i.p.)	4	22	−2.4±0.23*				
Chlorpromazine 10 mg/kg (i.p.)	8	22	−3.3±0.25*	2.5±0.53**	2.7±0.61**	−1.3±0.18**	0.04±0.03
Chlorpromazine 15 mg/kg (i.p.)	4	22	−4.5±0.35*				

* Significantly different from corresponding control values, $p<0.05$ (1-way analysis of variance). ** Significantly different from corresponding control values before the drug injection, $p<0.05$ (1-way analysis of variance). The values are expressed as the mean ± SEM.

rectal temperature and other thermoregulatory responses in response to either haloperidol or chlorpromazine application (figure 3). The ineffectiveness of these antipsychotic drugs at 29 °C T_a could be due to the fact that the effectors of heat loss were already maximally activated while their energy expenditure was not stimulated above their resting oxygen consumption[5,7,8]. It is intersting to note that both haloperidol and chlorpromazine suppress cold-induced thermogenesis, but do not decrease the resting energy expenditure in thermoneutral environment. Thus, it appears that haloperidol shares with chlorpromazine the ability to decrease heat production and to increase heat loss, both mechanisms resulting in decreasing rectal temperature; the presumed mechanism of action would be the same.

Most antipsychotic drugs such as haloperidol and chlorpromazine are thought to exert their therapeutic actions and to produce extrapyramidal side effects by blocking dopamine receptors[10]. However, several recent investigations showed that apomorphine, a dopamine receptor agonist, produced a fall, rather than a rise, in rectal temperature in rats[11,12]. In the cold (8 °C T_a), the hypothermia in response to apomorphine was due to a decrease in metabolism while at room temperature (22 °C T_a) the hypothermia was due to an increase in cutaneous temperature, an increase in E_{res} and a decrease in M[11]. This indicates that the hypothermia induced by haloperidol or chlorpromazine may not be solely mediated through the central dopaminergic mechanisms. In fact, our recent findings suggest that, in addition to brain dopamine, brain noradrenaline and serotonin play a role in the elaboration or modulation of hypothermia induced by chlorpromazine in rats[13,14]. For example, it was demonstrated that drugs potentiating dopaminergic transmission increased the chlorpromazine hypothermia, while drugs potentiating adrenergic transmission inhibited chlorpromazine hypothermia in rats[13]. Furthermore, depleting serotonin levels in brain with p-chlorophenylalanine, 5,6-dihydroxytryptamine or raphe lesions enhanced the chlorpromazine-induced hypothermia in rats[14]. In conclusion, the present results show that both haloperidol and chlorpromazine decrease heat production and increase heat loss and lead to hypothermia at room temperature (22 °C) and below it.

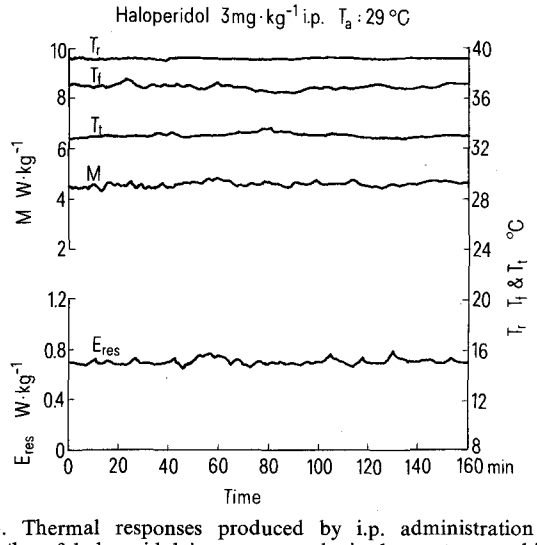

Fig. 3. Thermal responses produced by i.p. administration of 3 mg/kg of haloperidol in an unanesthetized rat at an ambient temperature (T_a) of 29 °C. T_r: rectal temperature; M: metabolic rate; T_f: foot skin temperature; T_t: tail skin temperature; E_{res}: respiratory evaporative heat loss.

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