these animals, the spinal cord was cooled for 6 days, about the normal duration of the febrile response, whereas in the other 10 the spinal cord was cooled for 28 days, the maximal duration of the disease. Body temperature was daily measured at noon with a thermocouple inserted about 60 mm beyond the anus. Oxygen consumption was determined, as required, by an open circuit method[3]. At various times of the day, but in each animal always at the same hour, the animals were placed in a metabolic cage; 30 min were allowed for the animals to quiet down and resting oxygen consumption was then determined for a further period of 30 min.

Results and discussion. In the days preceeding the infection, the body temperature of all animals averaged 37.5 ± 0.1 (SE)°C and the metabolic rate 7.6 ± 0.2 ml O_2/min. Cooling the spinal cord induced in the experimental animals a steady state increase in metabolic rate of $60.5 \pm 5.3\%$ ($p < 0.001$) but had no significant effect on body temperature.

The figure summarizes the results of the infection. The metabolic rate of the control animals increased by $28.6 \pm 3.5\%$ ($p < 0.001$) during the chill phase of fever and then it slowly decreased, being depressed by nearly 20% at the end of the febrile period. The metabolic rate of the experimental animals paralleled these changes at a higher level ($p < 0.001$) but it reached a maximum of only $66.1 \pm 4.8\%$ during the chill phase of fever. This suggests that the effects of fever and spinal cord cooling on heat production are not additive, probably because the thermosensitivity of the spinal cord, like that of the preoptic area[11], is reduced during fever. Despite this higher rate of heat production, the experimental and control animals had the same febrile temperatures. The survival of the experimental animals, however, exceeded that of the controls in each of the 5 independent series of experiments done and this effect was probably significant ($p = 0.06$, sets of contingency tables[12]).

These experiments thus show that the thermoregulatory increase in metabolic rate, which is considered detrimental for febrile patients because it increases the work of the heart and leads to the loss of weight, nitrogen and fluids[7], had no harmful effect on survival. Consequently, the detrimental effect of enhancing the febrile response by cooling the preoptic area[3] must be due either to some specific response elicited by cooling this region or, perhaps more likely, to the concomitant increase in body temperature - in cell cultures thermal injury may occur even at normal body temperatures[13] and high body temperatures are thought to inhibit various immunological responses[14].

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Blockade of nicotinic receptors in brain with d-tubocurarine induces decreased metabolism, cutaneous vasodilation and hypothermia in rats[1]

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Summary. Direct administration of d-tubocurarine into the lateral cerebral ventricle of conscious rats produced decreased metabolism, cutaneous vasodilatation and hypothermia at ambient temperatures of 8-22 °C. Also, pretreatment with d-tubocurarine antagonized the arecoline-induced hypothermia.

It has been repeatedly documented that intracranial administration of cholinomimetic drugs produces hypothermia in the rat[2-7]. This hypothermia can be antagonized by blockade of central muscarinic receptors with atropine sulfate[7]. The present study assessed the effects of blockade of central nicotinic receptors with d-tubocurarine on thermoregulatory responses and on the hypothermia induced by the cholinomimetic drug arecoline.

Materials and methods. Adult male Sprague-Dawley rats, weighing between 250 and 300 g, were used. The experiments were performed on unanesthetized animals restrained in rat stocks between 9.00 a.m. and 5.00 p.m. Between experiments the animals were housed individually in wire-mesh cages in a room at 25 ± 1.0 °C with a 12-h light-dark cycle. The animals were given free access to tap water and granular chicken feed. For the intracerebroventricular (i.c.v.) injection, a cerebroventricular cannula was implanted in each animal under general anesthesia (sodium pentobarbital, 6 mg/100 g, i.p.), the tip being located at the DeGroot[8] coordinates: AP, 7.0; L, 1.0; and 0.1 mm. A 27-gauge needle was connected via PE 10 tubing to a 50-µl Hamilton syringe. During the surgery the correct positioning of each guide tube was verified by the rapid flow of saline into the lateral cerebral ventricle under gravity. A period of 2 weeks was allowed to permit the animals to recover from the operation. The effects of d-tubocurarine (Sigma, 0.5-2.0 µg) and arecoline (Sigma, 50-200 µg) on metabolic, respiratory and vasomotor functions as well as body temperatures were assessed in a small animal partitional calorimeter[7,9-11]. Metabolic rate (M) was calculated from the animal's oxygen consumption and expressed as watts/kg body weight. Respiratory evaporative heat loss

(E_{res}) was calculated by measuring the increase in water vapor content in the expired air; E_{res} expressed as watts was calculated from evaporative water loss. Rectal (T_r), foot skin (T_f) and tail skin (T_t) temperatures were measured using thermocouples. All measurements were taken once per minute throughout the experiments, each variable being measured as a d.c. potential on a Hewlett-Packard digital voltmeter (DVM 3455) interfaced to an on-line CPU 9825 computer. Each minute all temperatures, M and E_{res} were calculated instantaneously by the computer and relayed immediately back to the laboratory where they were displayed by an on-line printer Hewlett-Packard 9871.

Results and discussion. Animals were permitted a period of 90 min at each level of T_a to attain thermal balance before the drug injections were made. Control injection of 5 µl of 0.9% saline into the lateral cerebral ventricle produced an insignificant change in thermoregulatory responses. However, i.c.v. administration of d-tubocurarine produced dose-dependent hypothermia at both 8 °C (0.5 µg, -0.2 ± 0.07 °C; 1.0 µg, -0.7 ± 0.08 °C; and 2.0 µg, -1.5 ± 0.11 °C) and 22 °C (0.5 µg, -0.3 ± 0.12 °C; 1.0 µg, -0.9 ± 0.09 °C; and 2.0 µg, -1.6 ± 0.12 °C). The hypothermia in response to d-tubocurarine was brought about by both decreased metabolic heat production and cutaneous vasodilatation (as estimated by an increase in both T_f and T_t) (fig. 1). In the heat (30 °C T_a), i.c.v. injection of d-tubocurarine produced an insignificant change in the thermoregulatory responses. The ineffectiveness of d-tubocurarine in the heat was because the effectors of sensible heat loss were already maximally activated, while the effector of heat production was already inactive[10,11]. On the other hand, i.c.v. injections of arecoline also produced dose-dependent hypothermia in rats at both 8 °C (50 µg, -0.8 ± 0.09 °C; 100 µg, -1.5 ± 0.14 °C; and 200 µg, -2.1 ± 0.18 °C) and 22 °C (50 µg, -0.6 ± 0.09 °C; 100 µg, $-1.1\pm0,12$ °C; and 200 µg, -1.8 ± 0.16 °C). At 8 °C T_a the hypothermia induced by arecoline was due to decreased metabolism only, while at 22 °C T_a the hypothermia was due to decreased metabolism, cutaneous vasodilatation and increased respiratory evaporative heat loss (fig. 2). The increase in E_{res} may be due to an increase in salivation. Furthermore, the table shows that the hypothermia induced by arecoline at both 8 and 22 °C T_a was strongly antagonized by pretreatment of animals with a small dose (0.5 µg, which has an insignificant effect on thermoregulatory responses) of d-tubocurarine (i.c.v.) or atropine sulfate (2 µg, i.c.v.). The present results showed that activation of central cholinergic receptors with arecoline inhibited heat production and/or facilitated heat loss which led to hypothermia in the rat. In addition, the arecoline-induced hypothermia was antagonized by pretreatment with either d-tubocurarine or atropine. This indicates that both the nicotinic and muscarinic receptors in the brain are responsible for the development of hypothermia in response to the administration of a cholinomimetic drug. However, blockade of central nicotinic receptors with d-tubocurarine (large doses) was also found to induce hypothermic responses in the rat. In fact, it has been suggested that blockade of central

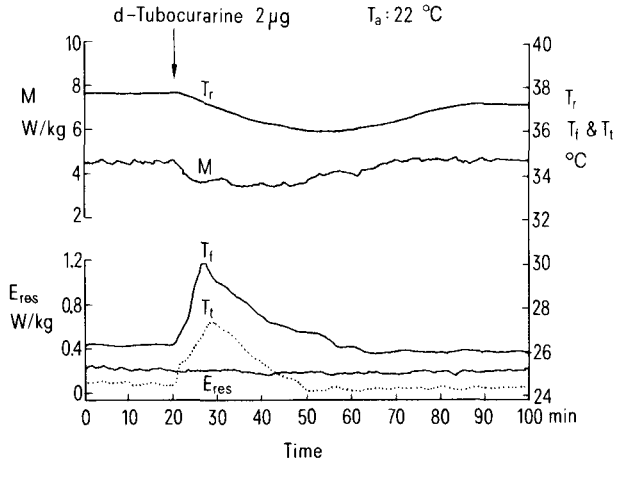

Fig. 1. The changes in rectal temperature (T_r), metabolic rate (M), foot skin temperature (T_f), tail skin temperature (T_t) and respiratory evaporative heat loss (E_{res}) produced by an injection of d-tubocurarine into the lateral cerebral ventricle of a conscious rat at an ambient temperature (T_a) of 22 °C.

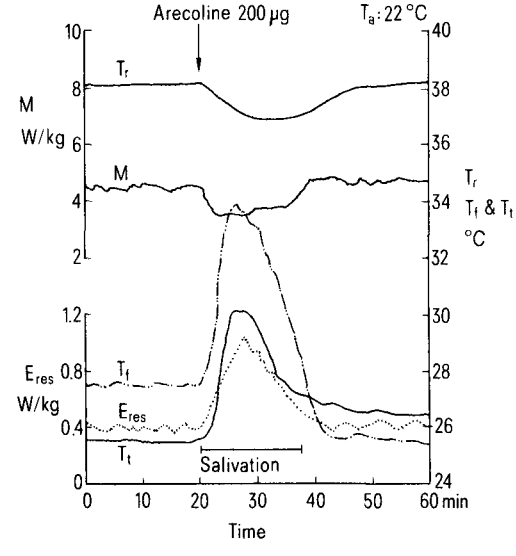

Fig. 2. The changes in rectal temperature (T_r), metabolic rate (M), foot skin temperature (T_f), tail skin temperature (T_t) and respiratory evaporative heat loss (E_{res}) produced by an injection of arecoline into the lateral cerebral ventricle of a conscious rat at an ambient temperature (T_a) of 22 °C.

Effects of d-tubocurarine and tropine sulfate treatment on the hypothermia induced by arecoline in the rat at ambient temperatures (T_a) of both 8 and 22 °C

Treatment of animals	Maximal changes in rectal temperature, Δ °C	
	$T_a = 8$ °C	$T_a = 22$ °C
1. 0.9% saline (l.c.v.) + arecoline 200 µg (l.c.v.)	-1.6 ± 0.12 (8)	-1.7 ± 0.15 (8)
2. d-Tubocurarine 0.5 µg (l.c.v.) + arecoline 200 µg (l.c.v.)	-0.7 ± 0.08* (8)	-0.8 ± 0.09* (8)
3. Atropine 2 µg (l.c.v.) + arecoline 200 µg (l.c.v.)	-0.8 ± 0.06* (7)	-0.5 ± 0.06* (7)

* Significantly different from corresponding control value, $p<0.05$ (Student's t-test). The values are expressed as the mean ± SEM, followed by the numbers of animals in parentheses. l.c.v. = lateral cerebral ventricle.

cholinergic receptors enhances the endogenous release of brain acetylcholine by blocking the presynaptic cholinergic receptors that are subjected to feedback inhibition by acetylcholine[12]. Therefore, it is likely that the hypothermia induced by d-tubocurarine was due to the enhanced release of acetylcholine in the brain.

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Reaching-related potentials in caudate nucleus and cerebellum of rats

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Summary. Electrical correlates of the lateralized reaching reaction were studied in rats with implanted electrodes. Averaged event-related potentials (ERPs) in the cerebellar dentate nucleus consisted of a negative wave coinciding with reach onset and followed 70 msec later by a positive deflection. The most prominent component of the more variable caudate ERPs was a negative wave culminating 60–120 msec after reach onset. The positive and negative ERP deflections corresponded to inhibitory and excitatory reactions respectively, at the single neuron level.

Rats trained to recover food pellets from a narrow tubular feeder perform the reaching movement the consistently with either left or the right forepaw[3]. The lateralized reaction has features of a ballistic movement[4] and is therefore well suited for electrophysiological analysis. Reaching is accompanied by unit activity changes in the motor cortex and caudate nucleus[5], and in the cerebellum[6]. Reaching-related EEG potentials are most pronounced in the motor cortex of the hemisphere contralateral to the preferred forepaw[7] and resemble event-related potentials (ERP) or motor potentials accompanying trained forelimb movements in the cat[8] or monkey[9,10]. The aim of the present study is to extend the ERP analysis of reaching in rats to basal ganglia and cerebellum.

15 male hooded rats were used. Under pentobarbital anesthesia (40 mg/kg), animals were bilaterally implanted with stainless steel electrodes (200 µm in diameter) placed in the heads of the caudate nuclei (AP 2, L 2, V 5) or in the dentate nuclei of cerebellum (AP 12, L 3, V 3) according to the stereotaxic atlas of Fifková and Maršala[11]. A silver screw (2 mm in diameter) in the nasal bone 7 mm rostral to the bregma served as the reference electrode. 2 silver electrodes were used to pick up the surface activity of the cerebellar hemispheres (AP 12, L 4). The leads were connected to a miniature 5-pin transistor socket and the whole implant was fixed to the skull bones with anchoring bolts and acrylate. Recording started 1 week after surgery.

Rats were trained to reach for 50-mg pellets of Larsen's diet placed 10–15 mm from the entrance of a narrow (11 mm in diameter) horizontal tube. Reaching was monitored by a photoelectric sensor, the output of which was used as the synchronization signal for a computer. The animal was connected through a counterbalanced 5-lead cable with the input of a conventional EEG apparatus with filters set to pass 1.5–200 Hz without attenuation. A LINC-8 computer was used for peri-event averaging (n = 32) of monopolar or bipolar records in a 768-msec interval starting 256 msec before reach detection. The position of the electrodes was histologically verified.

Cerebellar ERPs were obtained for 7 rats. Characteristic monopolar recordings are shown in figure 1. ERPs from the cerebellar cortex consisted of a protracted negative wave starting about 70 msec before reach onset and lasting approximately 200 msec. More complex ERPs were recorded in the dentate nucleus: a negative wave starting almost 100 msec before reach onset culminated during forelimb extension (-54 ± 8 µV, n = 7) and abruptly changed to a positive deflection ($+51 \pm 15$ µV, n = 7) with the maximum at 70 msec after reach onset. This waveform was sometimes followed by another sequence of negative-positive deflections. Bipolar recordings between the dentate nucleus and the cerebellar cortex stressed the components with opposite polarities which were most pronounced shortly after reach

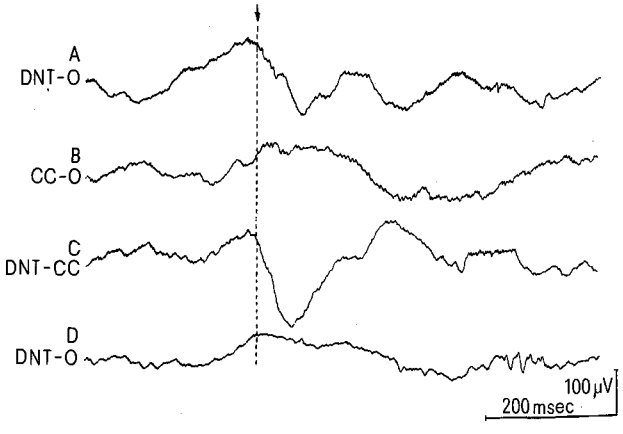

Figure 1. Averaged ERPs from the dentate nucleus (DNT) and cerebellar cortex (CC) ipsilateral to the reaching forepaw. Reach detection indicated by arrow. *A*, *B* Monopolar recordings; *C* bipolar recording; *D* ERP taken 24 h after electrolytic lesion of the recording site. The ERPs are averages of 32 responses. Calibration: 200 msec, 100 µV. Negativity upwards.