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A Discrete Mode of the Antipyretic Action of AVP, α-MSH and ACTH

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Summary

The antipyretic effect of AVP, α-MSH and ACTH consists in lowering the thrmoregulatory threshold and in shortening the time span of the fever. Thus, neuropeptides influence activity of hypothalamic neurones regulating body temperature. This was confirmed by recent experiments of Moravec (this volume) which indicate that spontaneous activity and thermosensitivity of neurones in hypothalamic slices can be influenced. by AVP. Why neuropeptides of different chemical structure such as AVT, on one hand, and α-MSH and ACTH, on the other hand, induce the same effect on thermoregulation remains to be elucidated.

Key words

Fever – AVP – α-MSH – Thermoregulatory thresholds

The antipyretic effect of some neuropeptides, namely that of AVP, α-MSH and ACTH, has been known for several years (Glyn and Lipton 1981, Lipton *et al.* 1981, Naylor *et al.* 1987). The detailed mode of action of these neuropeptides has not yet been described, however.

There are two possible ways by which the antipyretic effect of centrally administered neuropeptides can be realized:
1. Neuropeptides may inhibit the synthesis or action of prostaglandins, or of other endogenous pyrogens. 2. Neuropeptides may influence the activity of neurones directly involved in body temperature control and, in this way, they may lower the elevated threshold for induction of activity of individual thermoregulatory effectors occurring during fever.

In our experiments we concentrated on exploring the second possibility. The activity of thermoregulatory centres in the hypothalamus of the rabbit was analyzed by means of the method of intestinal cooling and intrahypothalamic injections of drugs (Janský *et al.* 1986). This method induces changes in central body temperature, while leaving the peripheral body temperature relatively unaffected. This makes it possible to express the activity of individual thermoregulatory effectors (cold thermogenesis, respiratory evaporative heat loss, peripheral vasomotor tone) as a simple function of changes in central body temperature, At the same time, this method makes it possible to make conclusions about changes in threshold body temperatures for induction of thermoregulatory effectors and about the thermosensitivity of the controlling centre, steeper slope in the curve indicating higher thermosensitivity and *vice versa*.

The same method can be also used to analyze the activity of thermoregulatory centres during fever. Fig. 1 shows the changes in thermoregulation in normal rabbits (A) and in rabbits during the early phase of fever (30 min after i.p. injection of endotoxin) (B). It is evident that during the early phase of fever an elevation of the threshold body temperature for induction of all thermoregulatory effectors occurs. There is no change in thermosensitivity of hypothalamic thermoregulatory centres, as judged from the unchanged slope of the curve.

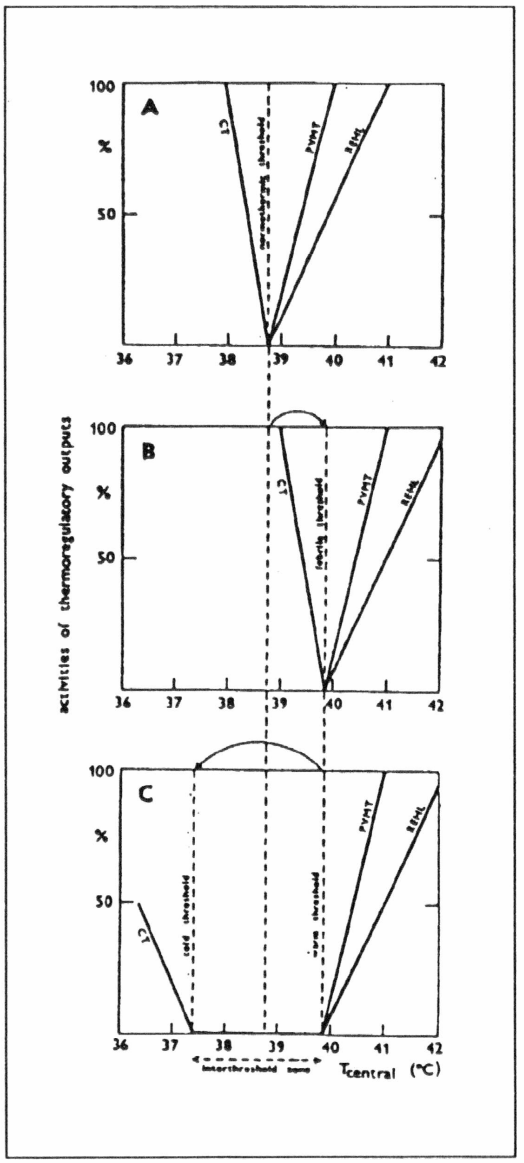

Fig. 1

Scheme of activation of thermoregulatory effectors (CT = cold thermogenesis, PVMT = peripheral vasomotor tone, REHL = respiratory evaporative heat loss) due to changes in central body temperature during intestinal cooling in normal rabbits (A) in febrile rabbits during the early phase of the fever (B) and in febrile rabbits during the late phase of the fever (C).

On the other hand, during the late phase of the fever (120 min after injections of endotoxin) (C) the threshold body temperature for induction of the peripheral vasomotor tone and respiratory evaporative heat loss remains elevated, while that for cold thermogenesis is shifted to low body temperatures, thus inducing a dissociation of thresholds for induction of warm and cold defence mechanisms (Vybíral *et al.* 1987).

The antipyretic effect of neuropeptides was analyzed after injection of 20 μg of AVP or α-MSH into the septum or into the anterior hypothalamus during the early phase of the fever. Fig. 2 shows that AVP induces similar changes as that observed in AVP-untreated rabbits during the late phase of fever, e.g. it lowers the threshold for cold thermogenesis and has no effect on the threshold for peripheral vasomotor tone and respiratory evaporative heat loss. Thus, AVP converts the first phase of fever into the late one and speeds up the time course of the entire febrile process. Similar results were obtained after injections of ACTH into the anterior hypothalamus (Vybíral *et al.* 1988).

The effect of α-MSH was slightly different from that of AVP and ACTH. α-MSH did not shift the threshold body temperature for induction of cold thermogenesis below the normal threshold, but rather returned the threshold to the nonfebrile level. In addition, α-MSH also slightly shifted the elevated threshold for peripheral vasomotor tone and respiratory evaporative heat loss to an almost normal level (Fig. 3). Thus, it appears that α-MSH eliminates fever faster than AVP.

In contrast to injections into the septum or anterior hypothalamus, injections of all neuropeptides studied into the posterior hypothalamus were without effect.

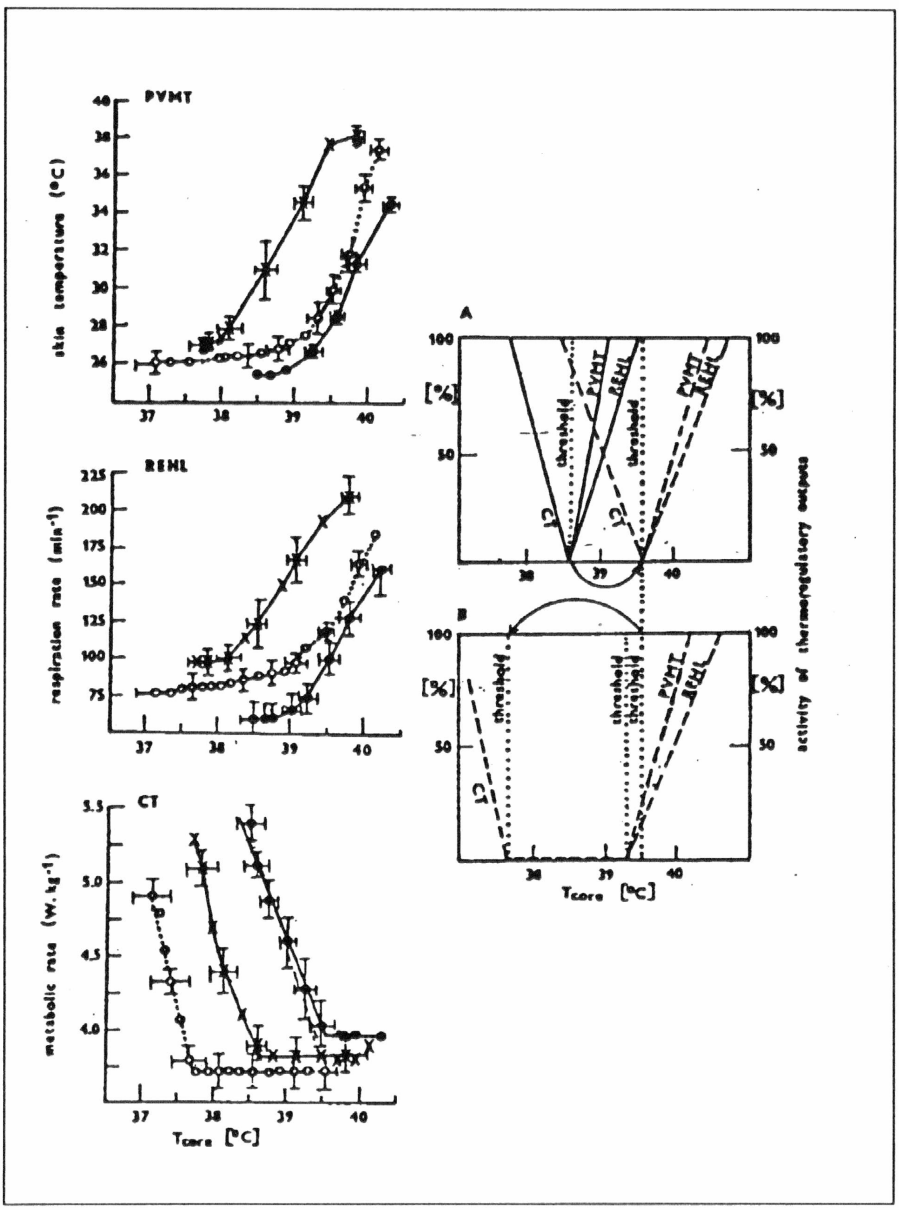

Fig. 2

Left side: Relationship between changes in body core temperatures due to intestinal cooling and intensities of peripheral vasomotor tone (PVMT), respiratory evaporative heat loss (REHL) and cold thermogenesis (CT) in control (- o -), in febrile (- o -) and in febrile rabbits after injections of 20 μg of AVP into the septal area (... o ...). Results represent averages and ± S.E.M. from 12 experiments performed on 6 rabbits. *Right side:* A. Scheme of activation of all thermoregulatory effectors in control (-) and febrile rabbits (---) due to changes in body core temperatures. B. Scheme of activation of all thermoregulatory effectors in febrile rabbits treated by 20 μg of AVP, due to changes in body core temperatures (---).

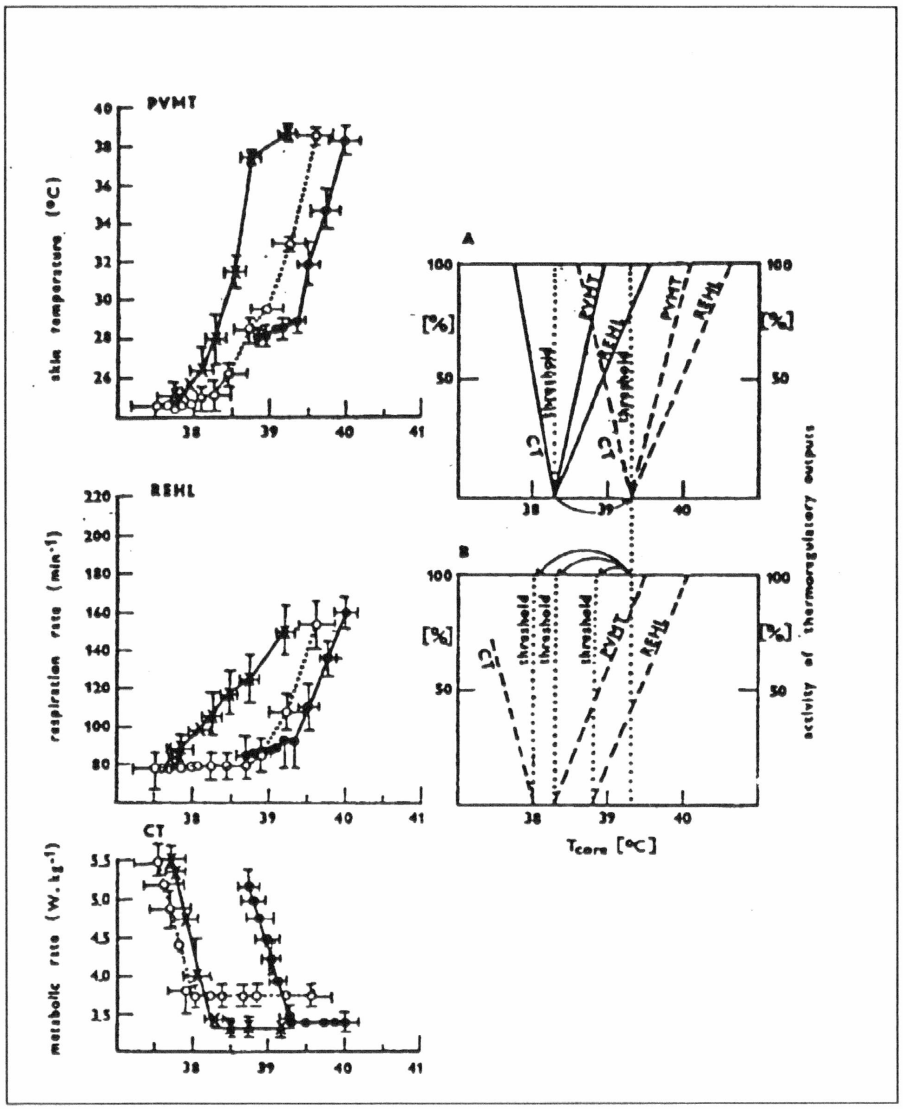

Fig. 3

Left side: Relationship between changes in body core temperatures due to intestinal cooling and intensities of peripheral vasomotor tone (PVMT), respiratory evaporative heat loss (REHL) and cold thermogenesis (CT) in control (- o -), in febrile (- o -) and in febrile rabbits after injection of 20 μg of a-MSH into the septal area (.. o ..). Results represent averages and ± S.E.M. from 6 experiments performed on 3 rabbits. *Right side:* A. Scheme of activation of all thermoregulatory effectors in control (-) and febrile rabbits (---) due to changes in body core temperatures. B. Scheme of activation of all thermoregulatory effectors in febrile rabbits treated by 20 μg of a-MSH due to changes in body core temperatures (---).

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Reprint Requests

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