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Hypothermia: Role of α_1- and α_2-Noradrenergic Receptors in the Hypothalamus of the Cat

R. D. MYERS[1], D. B. BELESLIN* AND AMIR H. REZVANI

Departments of Psychiatry and Pharmacology, and Center for Alcohol Studies
University of North Carolina, School of Medicine, Chapel Hill, NC 27514
*and *Department of Pharmacology, Medical Faculty*
University of Belgrade, P.O. Box 662, 11000 Belgrade, Yugoslavia

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MYERS, R. D., D. B. BELESLIN AND A. H. REZVANI. *Hypothermia: Role of α_1- and α_2-noradrenergic receptors in the hypothalamus of the cat.* PHARMACOL BIOCHEM BEHAV **26**(2) 373–379, 1987.—The purpose of this study was to characterize the α_1- and α_2-noradrenergic receptor sub-types which could mediate the hypothermic response produced by norepinephrine (NE) and other α-noradrenergic agonists applied to the thermosensitive zone of the hypothalamus. An array of four guide tubes was implanted stereotaxically so that their tips rested just above the anterior hypothalamic, preoptic area (AH/POA) of the cat. Following post-operative recovery, a micro-injection of an agonist or antagonist of NE receptors or control CSF vehicle was given in a volume of 1.0–2.0 μl in the AH/POA in each of the unrestrained cats. The α_1-noradrenergic receptor agonist, phenylephrine, but not methoxamine, applied to the AH/POA produced a dose-dependent hypothermia of up to 2.0°C. When applied similarly, the α_2-noradrenergic agonist clonidine, as well as norepinephrine, which acts on both α_1- and α_2-noradrenergic receptors, also induced a decline in the cat's core temperature of up to 1.5°C. The hypothermic response of clonidine was inhibited by pre-treatment of the AH/POA with a micro-injection of the selective α_2-noradrenergic blocking agent, yohimbine. However, yohimbine given similarly in the cat's AH/POA potentiated significantly both the phenylephrine and norepinephrine-induced hypothermia. The combined α_1-, α_2-noradrenergic receptor antagonist, phentolamine, also injected into AH/POA inhibited the thermolytic response evoked by both phenylephrine and norepinephrine, whereas it was virtually ineffective against the clonidine-induced hypothermia. These results, therefore, strongly suggest that both α_1- and α_2-noradrenergic receptors subserve the coordinated thermoregulatory mechanisms in AH/POA which are required for the functional dissipation of body heat and the consequent evocation of hypothermia.

Catecholamines Hypothermia Thermoregulation Micro-injection Phenylephrine Pre-optic area
Heat loss mechanisms Clonidine Cat Anterior hypothalamus Methoxamine α_1- and α_2-receptors
Body temperature Noradrenergic agonists and antagonists

IT is now well recognized that noradrenergic mechanisms in the anterior hypothalamic, pre-optic area (AH/POA) play a significant role in the thermoregulatory processes of most animals [6, 25, 33]. Numerous pharmacological studies have shown that norepinephrine (NE) micro-injected into the AH/POA causes a dose-dependent decline in the temperature of the cat [6, 11, 19, 32] and other species [23,24]. Further, hypothermia is produced also by the α_1-noradrenergic agonist, phenylephrine or the α_2-agonist, clonidine, similarly injected into the rostral hypothalamus of the cat and rat, respectively [32,38]. Other investigations on the antagonism between noradrenergic agonists and antagonists, delivered either into the AH/POA or intracerebroventricularly (ICV) in several species, also support strongly the view that α-noradrenergic receptors are involved in the mediation of the heat-loss pathway [5, 17, 29]. Of physiological significance is the fact that exposure to heat enhances the synaptic release of NE from the AH/POA of the unrestrained animal [27].

The existence of both α_1- and α_2-noradrenergic receptors in the central nervous system has been demonstrated by both radioligand binding and autoradiographic techniques [39, 40, 44, 45], and in hypothalamic tissue, a high density of α_2-receptor binding sites has been found [39]. In view of the potential role of receptors on noradrenergic neurons in the heat dissipating system [10, 24, 30], it is conceivable that either α_1- or α_2-noradrenergic binding sites in the AH/POA are involved in this functional component of the thermoregulatory mechanism. Therefore, the present investigation was undertaken in an attempt to characterize further the nature of localized α-noradrenergic receptors in AH/POA involved in the systemic process of heat dissipation by the use of agonists with a defined selectivity for α_1- and α_2-receptor sub-types [20]. In these experiments, carried out in the un-

[1]Requests for reprints should be addressed to Professor R. D. Myers, Medical Research Building A, 218-H, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

restrained cat, the potencies of the selective α_2-noradrenergic antagonist, yohimbine, as well as the less selective noradrenergic antagonist, phentolamine, were also investigated and compared.

METHOD

Neurosurgical Procedures

Adult female cats (n=4), weighing between 2.3–3.5 kg, were anesthetized with sodium pentobarbital given intravenously in a dose of 25–30 mg/kg. Utilizing aseptic techniques described previously [22], four 23-gauge stainless steel guide tubes were implanted stereotaxically in each animal following a set of coordinates [34] which encompassed the AH/POA. The position of the array was arranged bilaterally so that the tip of each guide tube rested 2–6 mm above the intended locus of micro-injection. A polystyrene pedestal was fastened to the skull by bone screws which were covered with cranioplastic cement. A protective cap served to protect the entire array, assure the patency of the indwelling cannulae and provide an aseptic preparation for the duration of the experiments [22]. Postoperatively, penicillin was administered for a period of 7 days after which the experiments were begun.

Micro-Injection Procedure

A YSI No. 401 thermistor probe was inserted into the colon of the animal to a depth of 10 cm and held in place by surgical tape wrapped gently around the base of the tail. After the cat's colonic temperature had stabilized for at least 1.0 hr, core temperature was recorded every 3 min for a period of 8–12 hr on a YSI telethermometer connected to a 6502-based microcomputer.

Each solution containing an agonist or antagonist was prepared just prior to a micro-injection in a pyrogen-free artificial CSF control vehicle which contained the chloride salts of Na^+, Ca^{2+}, K^+ and Mg^{2+} in an osmotically balanced proportion [21]. After the solution was passed through a sterilized Swinnex 0.22 μm millipore filter, the injector system was filled. Then a 27 ga stainless injector needle was inserted within the implanted guide tube to a predetermined depth. The test solution or the control CSF was delivered manually with a Hamilton 10 μl syringe over an interval of 10–15 sec. Each animal was then observed continuously for a period of two hr and intermittently for up to 24 hr.

Successive experiments were separated by an interval of 24–48 hr or longer. The specific treatment regimen for the micro-injection of the control CSF, an α-adrenergic agonist, or antagonist plus agonist was randomized so that each animal was included in each of the experimental conditions at least once. Before and after a set of experiments, 5.0 μg of NE was micro-injected into the AH/POA test site in the normothermic cat in order to verify the continued sensitivity of the locus to the catecholamine's hypothermic effect [25].

Drug Preparation

The following compounds were used in these experiments: NE HCl (Sigma); clonidine HCl (Sigma); 1-phenylephrine HCl (Sigma); methoxamine HCl (Sigma); yohimbine HCl (Sigma); phentolamine HCl (Ciba-Geigy); and alpha-methyl-p-tyrosine (α-MPT) methyl-ester (Sigma), a competitive inhibitor of tyrosine hydroxylase. Each compound was dissolved in the artificial CSF vehicle, except yohimbine HCl which was prepared in a 70% alcohol solution and diluted subsequently 1:4 in the control CSF. All of the drugs were micro-injected in a volume of 1.0 μl except yohimbine, phentolamine and α-methyl-p-tyrosine which were delivered in a volume of 2.0 μl. The dose of each drug refers to the salt and the range of the respective test concentrations was based on previous results from our laboratory as well as others [1, 19, 23, 32, 33].

Histological Verification

At the end of the experiments, the location of the sites of micro-injection was verified by means of standard histological procedures. After the animal was given an overdose of sodium pentobarbital, normal saline followed by 10% buffered neutral formalin (Fisher) was perfused retrograde through the abdominal aorta. The brain was removed, blocked and then frozen sections were cut on a cryotome at 100 μm and stained by cresyl violet following a method modified after Wolf [43]. The position of each micro-injection site was verified under light microscopy and mapped on anatomical reconstructions following standard procedures [23]. A representative histological section depicting a site of perfusion injection is presented in Fig. 1.

Statistical Analysis of Data

Student's t-tests were used to determine the significance of the difference between the control and each of the experimental test values. The results were considered statistically significant when $p = <0.05$.

RESULTS

A micro-injection of the control CSF vehicle in a volume of 1.0–2.0 μl exerted virtually no effect on the core temperature of the cat. During the first 90 min after injections, the mean maximum deviation in temperature following six control injections was 0.17±0.12°C (S.E.M.).

Noradrenergic Agonists-Induced Hypothermia

Three of four of the noradrenergic agonists micro-injected at sites located within the AH/POA, NE, clonidine, and phenylephrine, but not methoxamine, produced hypothermia. A composite analysis of the differential effects on core temperature of each of these agonists is presented in Fig. 2. With the exception of methoxamine, the mean maximum decline in the cat's temperature was dose-related. As illustrated in Fig. 3 (top), NE injected into this diencephalic region produced the typical, well-characterized hypothermic response [25], following a latency of less than 10 min. The hypothermia evoked by NE, which was dose-related linearly (n=31) in the range of 5.0–50.0 μg (Fig. 2), reached its maximum in approximately 1.0–2.0 hr after micro-injection, then persisted for up to 3–4 hr (e.g., Fig. 3, top).

As portrayed in Fig. 3, when phenylephrine (PHE) was micro-injected into the homologous region of the AH/POA, the cat's body temperature declined similarly to that following NE micro-injection. After a latency of 10 min, the hypothermic response reached its maximum level in approximately 1.0–2.0 hr and lasted for more than 3–4 hr (Fig. 3, bottom). The fall of body temperature caused by phenylephrine (n=29) was also dose-related linearly in the 5.0–50.0 μg

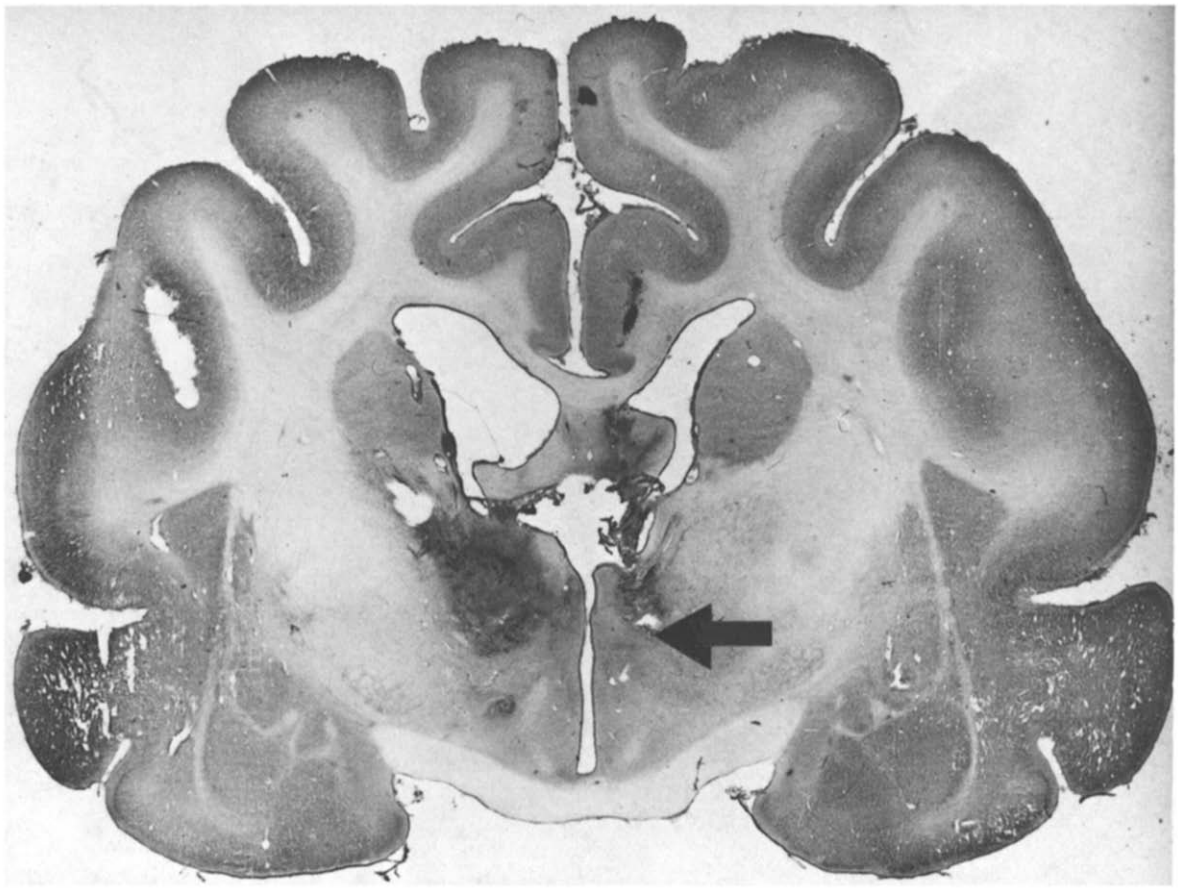

FIG. 1. Representative histological section depicting site (arrow) of 1.0–2.0 μl injector in the anterior of the hypothalamus of the unrestrained cat in coronal plane AP 13.0.

range (Fig. 2). In contrast to the thermolytic responses of NE and phenylephrine, 5.0 or 50.0 μg of methoxamine (MET) micro-injected at the same sites (n=8) in the AH/POA as the other α-noradrenergic agonists (Fig. 2) failed to produce a significant change in the core temperature of the cat (Fig. 3, bottom).

Although the micro-injection of 5.0–50.0 μg clonidine (CLN) into the AH/POA (n=44) produced a dose-related hypothermia (Fig. 2), the fall in the cat's body temperature was slow in onset, developing after a relatively long latency of 31.4±2.9 min. As shown in Fig. 3 (top), the clonidine-induced hypothermia reached its nadir in approximately 2.0 hr after its micro-injection and persisted ordinarily for more than 4.0 hr. In 8 of 44 experiments, the hypothermic response was followed by an overshoot in body temperature which is not uncommon among drugs which exert a central action on body temperature [26]. Clonidine-induced hypothermia often was preceded by a short-lasting set of autonomic responses including restlessness, licking, retching, emesis and mydriasis, which are described elsewhere [1].

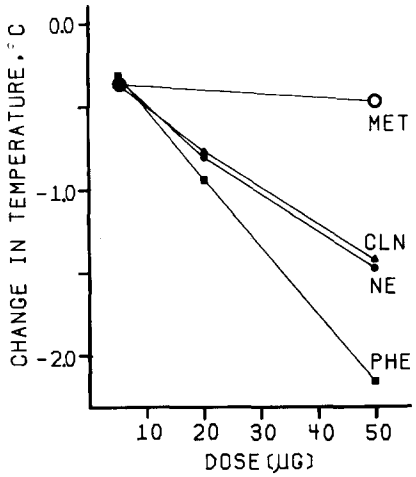

FIG. 2. Mean deviation in core temperature in unrestrained cats, following micro-injection of norepinephrine (NE), clonidine (CLN), phenylephrine (PHE) and methoxamine (MET) into AH/POA. The doses of α-noradrenergic agonists in μg are denoted in the abscissa. Each point represents the mean of 4–19 experiments.

Antagonists of Noradrenergic Hypothermia

In these experiments, the selective α-noradrenergic blocking agent, yohimbine (YOH), and the combined α_1- and α_2-noradrenergic antagonist, phentolamine (PHT), were

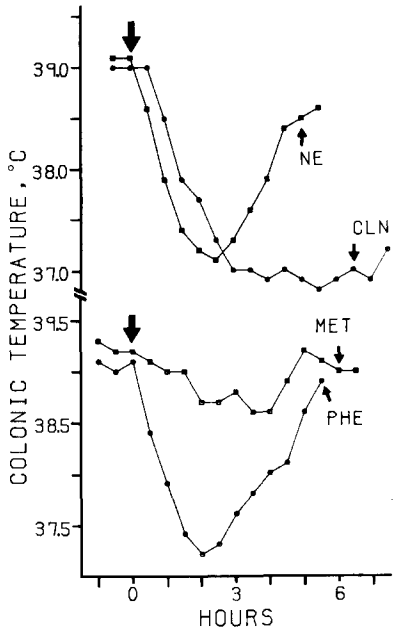

FIG. 3. Actual changes in colonic temperature in °C of two representative cats after micro-injection (arrow) at zero time of 20.0 μg of norepinephrine (NE) or clonidine (CLN) (top) and 50.0 μg of methoxamine (MET) or 20 μg phenylephrine (PHE) (bottom) in AH/POA.

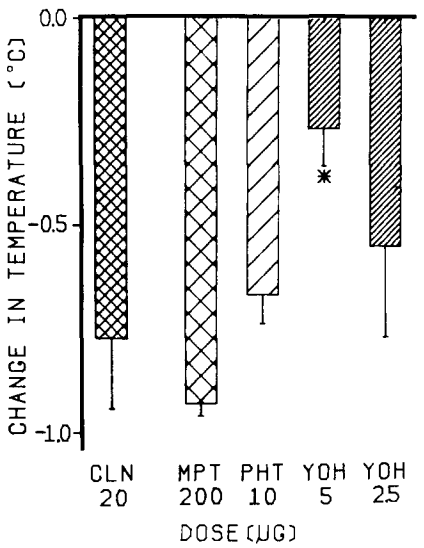

FIG. 4. Mean change±S.E.M. in core temperature of cats following 20.0 μg CLN in AH/POA as well as after pre-treatment of same micro-injection site with 2.5 and 5.0 μg YOH or 10.0 μg PHT, all given 15 min prior to CLN. α-MPT was given 2.0 hr before 20.0 μg CLN. S.E.M. denoted by vertical line of each column; significant difference from control of $p=<0.05$ denoted by asterisk. Number of experiments are as follows: CLN (n=18), α-MPT (n=4), PHT (n=3), 5.0 YOH (n=3), 2.5 YOH (n=4).

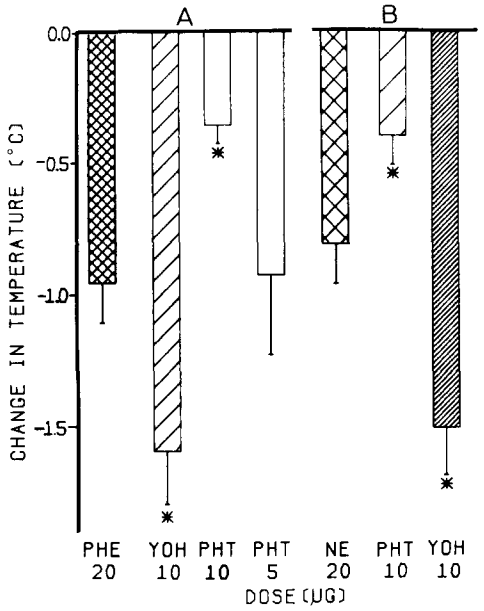

FIG. 5. Mean change±S.E.M. in core temperature of cats after: A, 20.0 μg PHE injected in AH/POA as well as after pre-treatment of same micro-injection site with 10.0 μg YOH and 10.0 or 5.0 μg PHT; B, 20.0 μg NE injected in AH/POA as well as after prior treatment of site with 10.0 μg PHT or 10.0 μg YOH. Each antagonist was micro-injected at the same site in AH/POA 15 min before the respective agonist. S.E.M. denoted by vertical line of each column; significant differences from control of $p=<0.05$ denoted by asterisk. Number of experiments are as follows: (A) PHE (n=19), YOH (n=3), 10.0 μg PHT (n=3), 5.0 μg PHT (n=3); (B) 20.0 μg NE (n=17), 5.0 μg PHT (n=4), 5.0 μg YOH (n=3).

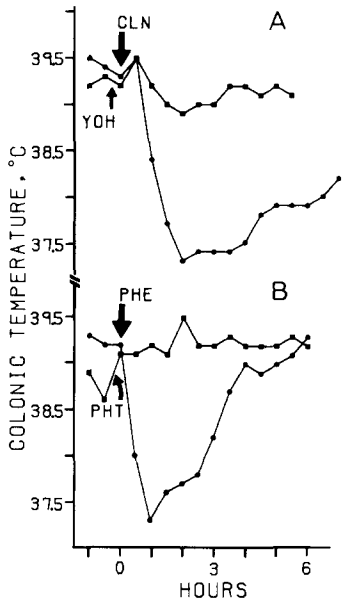

FIG. 6. Actual change in colonic temperature in °C of two representative cats after 1.0–2.0 μl injection of drug in AH/POA: A, 5.0 μg CLN (●) alone (second arrow) and after pre-treatment of same site with 20.0 μg YOH (first arrow) followed by the same dose of CLN (■); B, 20.0 μg PHE (●) alone (second arrow) and after pre-treatment of the same site with 10.0 μg PHT (first arrow) followed by same dose of PHE (■).

tested against the hypothermic response induced in the cat by NE, clonidine and phenylephrine.

When 2.5 μg yohimbine was micro-injected 15 min before 20.0 μg clonidine was delivered to the same AH/POA site, the antagonist inhibited slightly the agonist-induced hypothermia. However, as shown in Fig. 4, at the 5.0 μg dose, yohimbine significantly attenuated, $t(10)=2.79$, $p<0.05$, the thermolytic effect of clonidine. Conversely, when yohimbine was micro-injected in a dose of 10.0 μg 15 min before either 20.0 μg of either phenylephrine or NE at the same loci, the α_2-receptor antagonist potentiated significantly, by 0.6–0.7°C, both the phenylephrine, $t(8)=2.50$, $p<0.05$, and NE-induced hypothermia, $t(11)=3.12$, $p<0.01$. The mean changes in the cat's core temperature in response to the antagonist-agonist micro-injections into AH/POA are presented in Fig. 5 (A) for phenylephrine and Fig. 5 (B) for NE.

Phentolamine (PHT) was micro-injected in test doses of 5.0 and 10.0 μg 15 min before the similar injection in AH/POA of 20.0 μg phenylephrine, 20.0 μg NE and 20.0 μg clonidine. As presented in Fig 4, 10.0 μg phentolamine had no significant effect, $t(21)=0.75$, $p>0.05$, on the characteristic thermolytic responses induced in the cat by 20.0 μg of clonidine. In contrast, 10.0 μg phentolamine significantly inhibited the hypothermia, as illustrated in Fig. 5 A and B, produced in the cat either by 20.0 μg phenylephrine, $t(21)=3.02$, $p<0.01$, or 20.0 μg NE, $t(8)=2.28$, $p<0.05$, but in a dose of 5.0 μg had no significant effect, $t(21)=0.02$, $p>0.05$, on the phenylephrine-induced hypothermia (Fig. 5A).

The catecholamine synthesis inhibitor α-MPT was micro-injected in a dose of 200 μg 2.0 hr before 20.0 μg clonidine (n=4) at the same sites in the cat's AH/POA. As shown in Fig. 4, the clonidine-induced hypothermia was somewhat enhanced by α-MPT; however, the difference in the responses was not statistically significant, $t(21)=1.20$, $p>0.05$.

Representative experiments depicting the actual temperature changes over time following antagonist-agonist micro-injections in the cat's AH/POA are presented in Fig. 6. The antagonism of the clonidine (20.0 μg) hypothermia by 5.0 μg yohimbine was not entirely complete (Fig. 6A) in contrast to phentolamine's (10.0 μg) blockade of the thermolytic effect produced by phenylephrine (20.0 μg) (Fig. 6B).

DISCUSSION

As shown in the present experiments a differential decline in the core temperature of the cat is produced by different α-noradrenergic agonists, NE, clonidine and phenylephrine, when they are micro-injected directly into the animal's AH/POA. Overall, these findings agree with those which show that in most species, catecholamine agonists activate the thermoregulatory mechanism in the rostral portion of the hypothalamus which mediates the neuronal pathways underlying heat dissipation [6, 10, 23, 33, 38]. Nevertheless, several inconsistencies have been observed in connection with the central action on body temperature of different adrenoreceptor agonists [2,25]. For example, although NE injected ICV in the cat evokes a fall in temperature [5,10], clonidine given by the same route in the rat exerts no significant effect on the rodent's body temperature [38]. Although methoxamine injected ICV in the rabbit can evoke a slight rise in temperature [15], the present results show that this α_1-agonist micro-injected into the AH/POA of the cat, even in a dose as high as 50.0 μg, produces no effect on body temperature.

In the periphery, phenylephrine and methoxamine predominantly activate α_1-noradrenergic receptors [8, 9, 36], whereas clonidine selectively acts on α_2-noradrenergic receptors [37]. As revealed by the present experiments, both the α_1- and α_2-noradrenergic agonists, phenylephrine and clonidine, respectively, as well as NE acting on both receptor types, evoke hypothermia when they are micro-injected into the AH/POA. These results thus suggest that both subtypes of noradrenergic receptors in the hypothalamus are involved in the mediation of the heat loss system for the control of body temperature [25]. The differences in the action and potency of phenylephrine and methoxamine in the periphery in comparison to the AH/POA may reflect a unique characteristic of α-noradrenergic receptors in both central and peripheral nervous systems, as has been alluded to earlier [38].

The existence of both α_1- and α_2-noradrenoceptors in the central nervous system has been demonstrated by means of radioligand and autoradiographic techniques [39, 40, 44, 45]. In fact, a high density of α_2-noradrenoceptor binding sites apparently occurs in the hypothalamus of the rat [39]. Insofar as the mechanism underlying the proposed origin of the heat loss pathway [11], a relatively clear-cut differentiation of the agonist-antagonist relationship at the level of the AH/POA is demonstrated by these results. That is, yohimbine but not phentolamine inhibits the thermolytic response produced by clonidine injected into the cat's AH/POA. On the other hand, yohimbine potentiates the hypothermia induced by both NE and phenylephrine but phentolamine attenuates the decline in core temperature. In this connection, phentolamine given at sites in the AH/POA in doses 10 times greater than those used in this investigation abolishes the hypothermia induced by epinephrine when both substances are applied to an homologous hypothalamic region of the cat [32]. Surprisingly, phentolamine as well as yohimbine injected systemically can block the hypothermia evoked in the mouse by clonidine injected by the same route [42]. Although there is evidence that phentolamine principally blocks α_1-noradrenergic receptors [3,7], this antagonist in high doses can also act on α_2-noradrenoceptors as well [8]. Therefore, that phentolamine in a high dose may prevent the clonidine-induced hypothermia in the mouse is not an unexpected finding [42]. In view of the fact that yohimbine is a more selective α_2-noradrenoceptor antagonist than phentolamine [35], our findings on the yohimbine-clonidine as well as phentolamine-phenylephrine antagonism support a dual α_1-, α_2-noradrenoceptor mediation of the heat loss neurons located in the rostral hypothalamus [4]. Since the respective antagonistic actions of these drugs occur at relatively low concentrations of each drug infused, in comparison to an earlier study [32], a functional interpretation of these findings is thus strengthened further.

Of considerable interest is the yohimbine potentiation of the thermolytic action of both phenylephrine and NE within the AH/POA. One possible explanation of this observation is that yohimbine, in blocking the α_2-class of noradrenoceptors, serves to simultaneously cause a concomitant supersensitivity of the α_1-noradrenoceptors to both phenylephrine and NE. Alternatively, α_1-receptors in the neuronal system for thermoregulation could operate either in a manner opposite to that of the α_2-noradrenoceptors, or more likely, subserve a different component of the heat loss mechanism [33]. In fact, several recent reports have favored the view that

these adrenoceptor sub-types are antagonistic to one another in certain functions of the brain, including the central regulation of arterial blood pressure [14], locomotor activity [41] and feeding behavior [12].

In connection with the question of the synaptic mechanism of clonidine-induced hypothermia, the competitive inhibitor of tyrosine hydroxylase, α-MPT, micro-injected locally in the AH/POA prior to the α_2-agonist fails to prevent the response. Thus, the supposition that the thermolytic action of clonidine is mediated post-synaptically by α_2-noradrenergic receptors in the nerve terminals of the AH/POA rather than by pre-synaptic receptors is supported further. Although the receptors exist both pre- and post-synaptically [16], the likelihood that clonidine acts on post-synaptic membranes in the AH/POA is consistent with recent reports that post-synaptic α_2-receptors mediate specifically the distinct pharmacological actions of this agonist [12, 13, 28].

Finally, these observations raise the possibility from a physiological perspective that each of the two classes of noradrenergic receptors may mediate different neuronal systems in the rostral hypothalamus. For the processes of heat loss, these would include the excitation of vasodilation or inhibiton of vasoconstriction and the attenuation of metabolic heat production and shivering [4,26]. Thus, further research will be required to elucidate each of the specific functional components within the AH/POA which are responsible for the activation, perhaps by endogenous agonists [18,31], of different α-noradrenergic receptor sub-types which mediate the mechanism of heat loss in the animal.

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REFERENCES

1. Beleslin, D. B., A. H. Rezvani and R. D. Myers. Dissociation of locomotor impairment from mydriasis evoked by clonidine injected into cat's rostral hypothalamus. *Brain Res Bull* **17:** 379–385, 1986.
2. Bligh, J. *Temperature Regulation in Mammals and Other Vertebrates*. Amsterdam: North Holland, 1973.
3. Borowski, E., K. Starke, H. Ehrl and T. Endo. A comparison of pre- and postsynaptic effects of α-adrenolytic drugs in the pulmonary artery of the rabbit. *Neuroscience* **2:** 285–296, 1977.
4. Boulant, J. A. Hypothalamic control of thermoregulation: Neurophysiological basis. In: *Handbook of the Hypothalamus, Vol 3, Part A, Behavioral Studies of the Hypothalamus*, edited by P. J. Morgane and J. Panksepp. New York: Marcel Dekker, Inc., 1980, pp. 1–82.
5. Burks, T. F. Central alpha adrenergic receptors in thermoregulation. *Neuropharmacology* **11:** 615–624, 1972.
6. Cooper, K. E., D. L. Jones, Q. J. Pittman and W. L. Veale. The effect of noradrenaline, injected into the hypothalamus, on thermoregulation in the cat. *J Physiol* **261:** 211–222, 1976.
7. Doxey, J. C., C. F. C. Smith and J. M. Walker. Selectivity of blocking agents for pre- and postsynaptic α-adrenoceptors. *Br J Pharmacol* **60:** 91–96, 1977.
8. Drew, G. M. Effects of α-adrenoceptor agonists on pre- and post-synaptically located α-adrenoceptors. *Eur J Pharmacol* **36:** 313–320, 1976.
9. Drew, G. M. and S. B. Whiting. Evidence for two distinct types of postsynaptic α-adrenoceptor in vascular smooth muscle *in vivo*. *Br J Pharmacol* **67:** 207–215, 1979.
10. Feldberg, W. and R. D. Myers. Effects on temperature of amines injected into the cerebral ventricles. A new concept of temperature regulation. *J Physiol* **173:** 226–237, 1964.
11. Feldberg, W. and R. D. Myers. Changes in temperature produced by micro-injections of amines into the anterior hypothalamus of cats. *J Physiol* **177:** 239–245, 1965.
12. Goldman, C. K., L. Marino and S. F. Leibowitz. Postsynaptic α_2-noradrenergic receptors mediate feeding induced by paraventricular nucleus injection of norepinephrine and clonidine. *Eur J Pharmacol* **115:** 11–19, 1985.
13. Hamilton, T. C. and S. D. Longman. A comparison of the cardiovascular and sedative actions of the α-adrenoceptor agonists, FLA-136 and clonidine, in the rat. *Br J Pharmacol* **75:** 13–21, 1982.
14. Huchet, A.-M., M.-F. Doursout, J. Chelly and H. Schmitt. Possible role of central α_1-adrenoceptors in the control of the autonomic nervous system in normotensive and spontaneously hypertensive rats. *Eur J Pharmacol* **85:** 239–242, 1982.
15. Jones, D. L., W. L. Veale and K. E. Cooper. Thermoregulatory effects of methoxamine and isoprenaline following injections into the cerebral ventricles of conscious rabbits. *Can J Physiol Pharmacol* **55:** 821–827, 1977.
16. Langer, S. Z. Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* **32:** 337, 1981.
17. McLennan, P. L. The hypothermic effect of clonidine and other imidazolidines in relation to their ability to enter the central nervous system in mice. *Eur J Pharmacol* **69:** 477–482, 1981.
18. Meeley, M. P., P. R. Ernsberger, A. R. Granat and D. J. Reis. An endogenous clonidine-displacing substance from bovine brain: Receptor binding and hypotensive actions in the ventrolateral medulla. *Life Sci* **38:** 1119–1126, 1986.
19. Metcalf, G. and R. D. Myers. Precise location within the preoptic area where noradrenaline produces hypothermia. *Eur J Pharmacol* **51:** 47–53, 1978.
20. Molinoff, P. B. α- and β-adrenergic receptor subtypes properties, distribution and regulation. *Drugs* **28:** Suppl 2, 1–15, 1984.
21. Myers, R. D. General laboratory procedures. In: *Methods in Psychobiology*, Vol I, edited by R. D. Myers. London: Academic Press, 1971, pp. 27–65.
22. Myers, R. D. Methods for chemical stimulation of the brain. In: *Methods in Psychobiology*, Vol 1, edited by R. D. Myers. London: Academic Press, 1971, pp. 247–280.
23. Myers, R. D. *Handbook of Drug and Chemical Stimulation of the Brain: Behavioral, Pharmacological and Physiological Aspects*. New York: Van Nostrand Reinhold Company, 1974.
24. Myers, R. D. Hypothalamic control of thermoregulation: Neurochemical mechanisms. In: *Handbook of the Hypothalamus*, edited by P. Morgane and J. Panksepp. New York: Marcel Dekker, 1980, pp. 83–210.
25. Myers, R. D. Catecholamines and the regulation of body temperature. In: *Adrenergic Activators and Inhibitors*, edited by L. Szekeres. Heidelberg: Springer-Verlag, 1980, pp. 549–567.
26. Myers, R. D. The role of ions in thermoregulation and fever. In: *Handbook of Experimental Pharmacology*, edited by A. S. Milton. Heidelberg: Springer-Verlag, 1982, pp. 151–186.
27. Myers, R. D. and C. Chinn. Evoked release of hypothalamic norepinephrine during thermoregulation in the cat. *Am J Physiol* **224:** 230–236, 1973.
28. Nassif, S., E. Kempf, B. Cardo and L. Velley. Neurochemical lesion of the locus coeruleus of the rat does not suppress the sedative effect of clonidine. *Eur J Pharmacol* **91:** 69–76, 1983.
29. Preston, E. Central effects of α-adrenergic blocking agents on thermoregulation against venous blood-stream cooling in unanesthetized rabbits. *Can J Physiol Pharmacol* **51:** 472–481, 1973.

30. Reid, J. L., P. J. Lewis and M. G. Myers. Role of central dopaminergic mechanisms in piribedil and clonidine induced hypothermia in the rat. *Neuropharmacology* **14:** 215–220, 1975.
31. Rezvani, A. H., P. Huttunen and R. D. Myers. Effect of morphine and ethanol on neuronal release of norepinephrine from the hypothalamus: Relation to body temperature. *Ann NY Acad Sci* **473:** 516–519, 1986.
32. Rudy, T. A. and H. H. Wolf. The effect of intrahypothalamically injected sympathomimetic amines on temperature regulation in the cat. *J Pharmacol Exp Ther* **179:** 218–235, 1971.
33. Ruwe, W. D. and R. D. Myers. Dopamine in the hypothalamus of the cat: Pharmacological characterization and push-pull perfusion analysis of sites mediating hypothermia. *Pharmacol Biochem Behav* **9:** 65–80, 1978.
34. Snider, R. S. and W. T. Niemer. *A Stereotaxic Atlas of the Cat Brain*. Chicago: The University of Chicago Press, 1964.
35. Starke, K., E. Borowski and T. Endo. Preferential blockade of presynaptic α-adrenoceptors by yohimbine. *Eur J Pharmacol* **34:** 385–388, 1975.
36. Starke, K., T. Endo and H. D. Taube. Relative pre- and postsynaptic potencies of α-adrenoceptor agonists in the rabbit pulmonary artery. *Naunyn Schmiedebergs Arch Pharmacol* **291:** 55–78, 1975.
37. Starke, K., H. Montel, W. Gayk and R. Merker. Comparison of the effects of clonidine on pre- and postsynaptic adrenoceptors in the rabbit pulmonary artery. *Naunyn Schmiedebergs Arch Pharmacol* **285:** 133–150, 1974.
38. Tsoucaris-Kupfer, D. and H. Schmitt. Hypothermic effect of α-sympathomimetic agents and their antagonism by adrenergic and cholinergic blocking drugs. *Neuropharmacology* **11:** 625–635, 1972.
39. Unnerstall, J. R., I. Fernandez and L. M. Orensanz. The alpha-adrenergic receptor: Radiohistochemical analysis of functional characteristics and biochemical differences. *Pharmacol Biochem Behav* **22:** 859–874, 1985.
40. U'Prichard, D. C., M. E. Charness, D. Robertson and S. H. Snyder. Prazosin: Differential affinities for two populations of α-noradrenergic receptor binding sites. *Eur J Pharmacol* **50:** 87–89, 1978.
41. Velley, L., E. Kempf and B. Cardo. Locomotor activity of rats after stimulation of the nucleus locus coeruleus region or after lesion of the dorsal noradrenergic bundle: Effects of clonidine, prazosin and yohimbine. *Psychopharmacology (Berlin)* **78:** 239–244, 1982.
42. Von Voigtlander, P. F., H. J. Triezenberg and E. G. Losey. Interactions between clonidine and antidepressant drugs: A method for identifying antidepressant-like agents. *Neuropharmacology* **17:** 375–381, 1978.
43. Wolf, G. Elementary histology for neuropsychologists. In: *Methods in Psychobiology*, Vol I, edited by R. D. Myers. London: Academic Press, 1971, pp. 281–300.
44. Young, W. S. and M. J. Kuhar. Noradrenergic α_1 and α_2 receptors: Autoradiographic visualization. *Eur J Pharmacol* **59:** 317–319, 1979.
45. Young, W. S. and M. J. Kuhar. Noradrenergic α1 and α2 receptors: Light microscopic autoradiographic localization. *Proc Natl Acad Sci USA* **77:** 1696–1700, 1980.