diac ventricles are less heavily innervated and their A forming activity is predominantly from NMT (table). Sympathetically denervated tissues retain most or all of their A forming activity (fig. 1) and this A forming activity has the characteristics of NMT. These tissues appear to continue to synthesize A after sympathectomy because they contain A even after adrenal demedullation (fig. 2) and the A levels correlate with NMT activity. NMT activity increased after A levels were lowered by adrenal demedullation. Induction of NMT by low A levels may explain why A levels of rats increase with time following removal of the adrenal medullae[4] and why no symptoms develop when the adrenal medullae are absent.

A stimulates β_2 adrenergic receptors much better than do NA or dopamine. β_2 receptors are present on sympathetic nerves (where they enhance NA release) and blood vessels (where they vasodilate). Local A formation could affect the innervation and blood supply of many organs. Other endocrine systems, such as the renin angiotensin system, have local paracrine functions. A can be synthesized by many tissues and can stimulate adrenergic receptors in the same tissues, so A could have paracrine functions as well as endocrine functions. We found A forming activity in both human red (table) and white blood cells, so NMT activity can also be studied in humans.

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Depletion of hypothalamic norepinephrine reduces the fever induced by polyriboinosinic acid: polyribocytidylic acid (Poly I:Poly C) in rats[1]

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Summary. Administration of either Poly I:Poly C (0.05–0.50 μg) or norepinephrine (2–8 μg) into the anterior hypothalamic area produced a dose-related fever in rats. The fever induced by Poly I:Poly C was attenuated after selective depletion of norepinephrine in the hypothalamus. However, selective depletion of hypothalamic norepinephrine did not affect the fever induced by intrahypothalamic norepinephrine. The data indicate that Poly I:Poly C may act to induce fever through the endogenous release of norepinephrine from the rat's hypothalamus.
Key words. Hypothalamus; norepinephrine; fever; pyrogen; polyriboinosinic acid; polyribocytidylic acid.

Evidence has accumulated to indicate that human alpha interferon (IFN) meets the criteria for being an endogenous pyrogen[2–4]. It produces a brisk, monophasic fever following injection, is free of endotoxin, and increases the production of prostaglandin E-2 from brain tissue in vitro and in vivo. Furthermore, when the homopolymer duplex of Poly I:Poly C, an IFN inducer, was injected i.v., it was shown to induce fever accompanied by the appearance of high titers of IFN in rabbits[5]. In contrast, equivalent doses of Poly I:Poly C alone were not pyrogenic. Recently, both in the rabbit[6] and the rat[7], microinjection of Poly I:Poly C or IFN into the anterior hypothalamic area was also shown to produce fever.

It should be noted that the latency of onset for fever was about 60 min after an intravenous dose, or about 30 min after an intrahypothalamic dose of Poly I:Poly C or IFN. Such a long latency indicates that IFN or its inducer may act through the endogenous release of intermediary pyrogenic factors to induce fever. Indeed, it has been shown that the IFN-induced or Poly I:Poly C-induced fever may be due to the local release of a prostaglandin or a protein factor of unknown chemical nature in the hypothalamic area. Further, a recent report demonstrated that depletion of norepinephrine in the rat's hypothalamus reduced the fever induced by prostaglandin E-2[8]. This raises the possibility that the noradrenergic pathways in the hypothalamus are involved in the genesis of fever induced by IFN or its inducer Poly I:Poly C. In order to deal with this question, in the present study 6-hydroxydopamine (6-OHDA) was used to destroy the

catecholaminergic nerve terminals in the hypothalamus, thus reducing their catecholamine levels, and the alterations in the febrile responses to Poly I:Poly C in unanesthetized rats were then assessed.

Materials and methods

Experiments were performed on male Sprague-Dawley rats weighing between 250 and 300 g. The animals were fed with a dry powder chow. They were housed individually in wire-mesh cages in a room maintained at 22 ± 1.0 °C with a 12 h: 12 h light-dark cycle. For administration of Poly I:Poly C (0.05–0.50 µg; Pharmacia Molecular Biologicals, Uppsala, Sweden), norepinephrine (2–8 µg; Sigma Chemical Co., Saint Louis, MO, USA), 6-OHDA hydrobromate (10–50 µg; Sigma), 0.9% saline, or 0.9% saline plus 0.1% ascorbic acid into the anterior hypothalamus, a cannula guide tube with trocar was implanted using the stereotaxic atlas and coordinates of Paxinos and Watson [9] in animals under pentobarbital sodium (60 mg/kg, i.p.) anesthesia. A solution of 6-OHDA was made by dissolving the drug in 0.9% saline plus 0.1% ascorbic acid. The following coordinates were used: A 7.2, L 0.3–0.8, and H 0.7–1.2 mm. After two self-tapping screws had been attached to the calvarium of the parietal bones, the cannula guide tubes were inserted to the desired depth through the craniotomy holes. They were anchored with dental cement to the cranial surface, which had been scraped clean of periosteum.

A period of 2 weeks was allowed to permit the animals to recover from surgery. At the time of injection, the cannula insert was connected to a 10-µl Hamilton microsyringe by PE 10 polyethylene tubing. The volume of injection down each cannula was 1.0 µl. In the present study, separate rats were used for each drug injection. Rectal temperature was measured with a copper-constantan thermocouple enclosed in PE 200 tubing, sealed at one end, inserted 60 mm into the rectum. All measurements were taken once per minute throughout the experiments, with a d.c. potential on a Hewlett-Packard digital voltmeter (DVM 3455) interfaced to an on-line computer (Hewlett-Packard 9825). For each minute, all temperatures were displayed on an on-line printer (Hewlett-Packard 9871). At the end of some experiments, animals were decapitated and their hypothalami were rapidly removed and frozen on solid CO_2. Later, tissues were homogenized in 0.4 N $HClO_4$, and norepinephrine and dopamine were extracted by alumina column chromatography and quantified by spectrophotofluorometry as described previously [10]. Animals were kept at an ambient temperature of 22 °C for at least 90 min so that they would attain thermal balance before drugs were administered. Calculations were made of the maximal elevation of rectal temperature over the pre-injection level (△ °C), and of the thermal index, the area under the curve produced in the 60-min period after the injection of drug in terms of °C/h [11]. The significance of the difference between means was determined by one-way analysis of variance. A value of $p < 0.05$ was taken to be significant.

Results and discussion

Table 1 contains a summary of the effects of intrahypothalamic administration of 6-OHDA on the hypothalamic content of norepinephrine and of dopamine. Two intraphypothalamic injections of 50 µg of 6-OHDA, at intervals of 2 days, caused a significant depletion of norepinephrine to 30.51% of the control value of norepinephrine, and of dopamine to 41.58% of the control level in the hypothalamus. On the other hand, 3 intrahypothalamic injections of 10 µg of 6-OHDA at intervals of 2 days caused a significant depletion of norepinephrine, to 22.76% of control, while the dopamine content was not significantly reduced (96.90% of control). Table 2 contains a summary of the febrile responses of the rats which received 3 intrahypothalamic injections of 10 µg of

Table 1. Effects of intrahypothalamic administration of 6-OHDA on the hypothalamic contents of norepinephrine and dopamine of the rat (mean ± SFM)

Treatment	n	Hypothalamic content (ng/gtissue) Norepinephrine	Dopamine
0.9% saline + 0.1% ascorbic acid	6	980 ± 90	392 ± 17
6-OHDA 2×50 µg[a]	6	299 ± 41*	163 ± 25*
6-OHDA 3×10 µg[a]	6	223 ± 34*	380 ± 27

[a] Doses injected intrahypothalamically 2 days apart; rats were killed 14 days after first injection. *Significantly different from control values (vehicle group), at $p < 0.05$ (one-way analysis of variance). n = Number of rats tested.

Table 2. Effects of intrahypothalamic pretreatment of rats with 6-OHDA on the fever induced by intrahypothalamic injection of Poly I:Poly C or norepinephrine in rats (mean ± SFM)

Treatments	Peak elevation of rectal temperature (△ °C)	Thermal index °C/h
Vehicle-treated rats[a]:		
0.9% saline (n = 7)	0.21 ± 0.05	0.07 ± 0.04
Poly I:Poly C 0.05 µg (n = 5)	0.72 ± 0.06*	0.31 ± 0.06*
Poly I:Poly C 0.25 µg (n = 7)	1.38 ± 0.12*	0.65 ± 0.09*
Poly I:Poly C 0.50 µg (n = 5)	1.64 ± 0.07*	0.79 ± 0.17*
Norepinephrine 2 µg (n = 6)	0.54 ± 0.05*	0.29 ± 0.07*
Norepinephrine 4 µg (n = 6)	0.87 ± 0.06*	0.48 ± 0.08*
Norepinephrine 8 µg (n = 6)	1.21 ± 0.08*	0.61 ± 0.13*
6-OHDA-treated rats[a]:		
0.9% saline (n = 8)	0.18 ± 0.06	0.08 ± 0.05
Poly I:Poly C 0.05 µg (n = 5)	0.25 ± 0.05**	0.10 ± 0.05**
Poly I:Poly C 0.25 µg (n = 8)	0.64 ± 0.07**	0.28 ± 0.09**
Poly I:Poly C 0.50 µg (n = 5)	0.67 ± 0.08**	0.35 ± 0.07**
Norepinephrine 2 µg (n = 6)	0.63 ± 0.06	0.26 ± 0.05
Norepinephrine 4 µg (n = 6)	0.89 ± 0.07	0.44 ± 0.07
Norepinephrine 8 µg (n = 6)	1.18 ± 0.07	0.56 ± 0.12

[a] Animals received three doses of vehicle (0.9% saline + 0.1% ascorbic acid) or 6-OHDA (10 µg) at intervals of 2 days; Poly I:Poly C, norepinephrine or saline was given 7–14 days after first injection of vehicle or 6-OHDA. *Significantly different from control values (saline group), at $p < 0.05$ (one-way analysis of variance). **Significantly different from control values (vehicle group), at $p < 0.05$ (one-way analysis of variance).

6-OHDA to intrahypothalamic administration of norepinephrine or Poly I:Poly C, and a comparison of these responses with those of vehicle-treated animals. It was found that selective depletion of hypothalamic norpinephrine significantly reduced the Poly I:Poly C-induced fever. However, the fever induced by intrahypothalamic injections of norepinephrine was not affected by selective depletion of hypothalamic norepinephrine.

Thus, it appears that noradrenergic pathway occurs in the hypothalamus which mediates the febrile responses to Poly I:Poly C or IFN. In the present results, the febrile responses to Poly I:Poly C may be related to the endogenous release of norepinephrine from the rat's hypothalamus. Intrahypothalamic injection of Poly I:Poly C may have resulted in activation of hypothalamic noradrenergic receptors and thus cause febrile responses. The Poly I:Poly C-induced, but not the norepinephrine-induced, fever would be prevented by depletion of hypothalamic norepinephrine. Norepinephrine injected intrahypothalamically is believed to act on postsynaptic adrenergic receptors in the hypothalamus to induce fever. The results are supported by the findings of many investigators. For example, intrahypothalamic injection of norepinephrine or other adrenergic agonists caused febrile responses[12,13]. The norepinephrine-induced fever was antagonized by pretreatment of the rat's hypothalamus with adrenergic receptor antagonist[12]. Microiontophoretic application of norepinephrine reduced the activity of warm-sensitive units in the hypothalamus, whereas the discharge rate of cold-sensitive units in the rat's hypothalamus was elevated[14]. Recently, our pilot study also demonstrated that the Poly I:Poly C-induced fever was underpinned by central administration of adrenoreceptor blocking agents (Lin et al., unpublished data).

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Thermoadaptive influence on reactivity pattern of vasopressinergic neurons in the guinea pig.

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Summary. In cold-adapted guinea pigs, increased amounts of arginine-vasopressin (AVP) immunoreactive material could be visualized in neurons of the supraoptic and paraventricular nucleus, in fibers projecting to the neurohypophysis and in fiber terminals in the ventral lateral septum and in the amygdala. In warm-adapted animals the reactivity to AVP antiserum was poor in all neuronal structures examined. High AVP-immunoreactivity was accompanied by a reduced febrile response to bacterial pyrogen in cold-adapted guinea pigs.
Key words. AVP; immunohistochemistry; nucl. paraventricularis and supraopticus; ventral lateral septum; thermal adaptation; antipyresis; guinea pig.

In a previous study[1] we found that in guinea pigs peripheral release of AVP is dependent on ambient temperature. In animals born and reared at 22 °C the level of AVP in arterial plasma was 3.2 pg AVP/ml, and in 24-h urine samples 6.8 ng AVP/day. Adaptation to 5 °C caused a 2–3-fold increase of AVP concentration in blood plasma and an 8–10-fold increase in daily excreted amounts of AVP. Adaptation to 28 °C was accompanied by a 20–30% reduction of AVP in blood plasma and in 24-h urine, compared with values at 22 °C. The influence of these thermoadaptive changes in peripheral release of AVP on the water-balance in guinea pigs has already been described in detail[1].

A high release of AVP into different parts of the central nervous system has been postulated for other physiological situations as well. Increased amounts of vasopressinergic material could be demonstrated immunocytochemically in the septum and amygdala of guinea pigs at the