Cyclic AMP generation in hypothalamus of hypertension-prone and -resistant rats

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Summary

1. The noradrenaline-induced accumulation of cyclic AMP is decreased in both the anterior and the posterior hypothalamus of hypertension-prone as compared with resistant rats, but is similar in the cortex.

2. The nonadrenaline-induced accumulation of cyclic AMP is decreased in the posterior hypothalamus as compared with the anterior hypothalamus of both strains.

3. The decreased sensitivity to phosphodiesterase inhibitor in the hypothalamus of hypertension-prone as compared with resistant rats suggests that strain differences in phosphodiesterase activity may exist.

4. Since differences in cyclic AMP were found in the hypothalamus and the medulla oblongata, regions involved in blood pressure control, but not in the cortex, they may be relevant to the diverse susceptibility to hypertension of hypertension-prone and resistant rats.

Key words: cyclic AMP, genetically hypertensive rats, hypothalamus, noradrenaline, phosphodiesterase.

Introduction

Recent studies indicate that cyclic AMP may be involved in the central regulation of blood pressure (Walland, 1975; Walland, 1977). However, present knowledge of the role of brain cyclic AMP in hypertension is scant and controversial. The cyclic AMP content in the hypothalamus of genetically hypertensive rats (SH rats) as compared with normal controls was reported decreased (Schmid, Hempel & Heidland, 1978), although in another study increased levels were found (Volicer, O'Donnell, Chase & Gavras, 1979).

Since noradrenaline is an important central neurotransmitter, we have compared the noradrenaline-induced accumulation of cyclic AMP in brain areas of hypertension-prone (H) and hypertension-resistant (N) rats developed in our laboratory (Ben-Ishay, Saliternick & Welner, 1972).

Methods

Male rats (250 g) were decapitated, and the brains rapidly dissected on ice. Tissue slices 1 mm³ obtained from the hypothalamus and the medulla oblongata, regions involved in blood pressure control, but not in the cortex, they may be relevant to the diverse susceptibility to hypertension of hypertension-prone and resistant rats.

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Cyclic AMP in the rat hypothalamus

**FIG. 1.** Accumulation of cyclic AMP induced by noradrenaline in the hypothalamus of hypertension-prone (H) and hypertension-resistant (N) rats. The difference between H and N rats was significant in each segment, and the difference between the anterior and the posterior segments was significant in each strain (P < 0.01). Blood pressures were: H, 139 ± 5 mmHg; N, 115 ± 6 mmHg (P < 0.01). *P < 0.01.

12 min⁻¹ mg⁻¹ of protein in H rats vs 215 ± pmol 12 min⁻¹ mg⁻¹ of protein in N rats, P < 0.01. In the cortex, the response was comparable, the respective values being 64 ± 5 and 55 ± 6 pmol 12 min⁻¹ mg⁻¹ of protein.

The accumulation of cyclic AMP was significantly lower in both the anterior and the posterior hypothalamus of H as compared with N rats (P < 0.01) (Fig. 1). In both strains, the accumulation of cyclic AMP was significantly higher in the anterior than in the posterior hypothalamus (P < 0.01). In the presence of increasing doses of phosphodiesterase inhibitor, the cyclic AMP accumulation in response to noradrenaline was different in H and N rats. Whereas in N rats 15 μmol of RO 20-1724/1 sufficed to achieve maximal rise in cyclic AMP, in H rats 30 μmol/l was needed to obtain the same effect.

**Discussion**

In the present study the accumulation of cyclic AMP induced by noradrenaline was significantly lower in the hypothalamus of H rats than in that of N rats. The results indicate that strain differences may exist in the noradrenaline-sensitive cyclic AMP-generating system.

Previous workers have ascribed a central depressor function to the anterior part of the hypothalamus, and a pressor function to the posterior part (Brody, Fink, Buggy, Haywood, Gordon, Knupfer, Mow, Mahoney & Johnson, 1979; Calaresu & Ciriello, 1979). The noradrenaline-sensitive cyclic AMP-generating system was therefore compared in the anterior and the posterior hypothalamus of H and N rats. The noradrenaline-induced accumulation of cyclic AMP was significantly lower in both the anterior and the posterior hypothalamus in H rats, and significantly lower in the posterior than in the anterior segment in each strain.

It has previously been shown that the noradrenaline-sensitive cyclic AMP-generating system can be modified by the available concentration of neurotransmitter (Schwartz, Costentin, Martres, Protais & Baudry, 1978). Our results suggest that the postsynaptic stimulation by noradrenaline in vivo may be higher in H than in N rats, in both segments of the hypothalamus. It also seems to be higher in the posterior than in the anterior segment in both strains.

The findings in the hypothalamus of H and N rats are interesting in view of our previous report of an increased sensitivity of the noradrenaline-sensitive cyclic AMP-generating system in the medulla oblongata of H rats (Ben-Ishay, Kobrin, Ebstein & Belmaker, 1979). Dismukes & Mulder (1976) have suggested that cyclic AMP generated by adenyl cyclase, linked to different receptors, may play antagonistic roles in different neurons. Our finding of diametrically opposed sensitivity of the cyclic AMP-generating system in the hypothalamus and the medulla oblongata appears to be in keeping with this concept.

Since differences in cyclic AMP accumulation may be related to different rates of degradation, the phosphodiesterase activity was assessed in the presence of increasing doses of a phosphodiesterase inhibitor. The results obtained suggest that strain differences in phosphodiesterase activity may account for the difference in cyclic AMP accumulation. Whether the different phosphodiesterase activity is primary or secondary to different rates of cyclic AMP production remains to be established.

The relevance of our findings to the diverse susceptibility of H and N rats to hypertension remains to be proven. The difference in cyclic AMP accumulation observed in the hypothalamus and the medulla oblongata (Ben-Ishay et al., 1979) of H and N rats are in contrast to the
finding of comparable cortical cyclic AMP values. Since both the hypothalamus and the medulla oblongata participate in blood pressure regulation, we postulate that these differences may be relevant to the diverse susceptibility to hypertension of our strains.

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References


