The significance of an increase in myocardial cyclic AMP in response to hypoxia is presently unresolved. It has been repeatedly suggested that cyclic AMP is the intracellular agent mediating the inotropic action of adrenergic amines. However, in the hypoxic state cardiac muscle is largely depleted of its high energy intermediates[5,6,13,14] and, hence, would be unable to respond to an increase in cyclic AMP content with increased contractility. The role of cyclic AMP in the conversion of glycogen phosphorylase from the b- to the more active a-form has been also well-documented. Therefore, an increase in cyclic AMP levels in the hypoxic heart might be interpreted as an attempt by the myocardium to overcome the energy depletion due to oxygen deprivation by activation of glycogen phosphorylase. Meerson[15] has suggested that the common condition preceding the initiation of cardiac hypertrophy by various causes, including work overload and hypoxia, is a relative energy deficit. He has further suggested that cyclic AMP might provide the biochemical link between energy deficit and increased RNA and protein synthesis. However, the mechanism whereby energy depletion leads to alterations in cyclic nucleotide levels has not been established.

The inherent difficulty of directly correlating increased cyclic AMP content with increased RNA synthetic activity in the perfused heart led us to investigate the effect of cyclic nucleotides on RNA synthesis in isolated myocardial nuclei. We have observed that cyclic AMP significantly stimulates the activity of RNA polymerase under conditions of low ionic strength in the presence of magnesium ion in this system (manuscript in press).

Information regarding levels of cyclic GMP in cardiac tissue has been limited to the reciprocal relationship between cyclic AMP and cyclic GMP during the contraction cycle of frog hearts beating at low rates[16], and to the demonstration of an increase in cyclic GMP associated with a decrease in contractility in the isolated perfused heart following administration of acetylcholine[17,18]. The significance of a decrease in myocardial cyclic GMP in response to hypoxia noted in this study requires additional investigation.

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Cerebral application of enkephalins

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Summary. Implantation of enkephalins A or B into the ventral thalamus or injection into the lateral ventricle of rats evoked only weak signs of stereotyped behavior, but did not cause gnawing.

Since the discovery and structure-determination of enkephalins[1,2], these pentapeptides have become available by synthesis[3]. The high biological activity of these peptides is usually demonstrated in vitro by their morphine-like activity on the guinea-pig ileum or on the mouse vas deferens[1,4]. In vivo applications are, however, handicapped by the fact that the peptides undergo rapid enzymatic hydrolysis[2].

We have shown recently that deposition of small amounts of morphine (50–100 µg on each side) into the ventral thalamus evokes stereotyped behavior in rats[5]. This is a stimulatory effect and is easily recognisable. Still smaller amounts of the alkaloid are effective if injected into the lateral ventricle of the rat[6]. Since in such topical applications the chances of metabolic survival are greater – e.g. the CSF is known to have a very low level of proteins and of enzymic activities – we have tried both implantation of 20 or 50 µg into the ventral thalamus and intraventricular injection of 10 or 50 µg, using (methionin-)enkephalin A as well as (leucine-)enkephalin B. On the basis of in vitro experiments[1,2], these amounts should be equivalent to the same or larger doses of morphine. For each dosage, 10 male rats of 150–200 g body weight were used. For implantation into the thalamus, aqueous solutions of the peptides were mixed with talc and the material was dried at room temperature. For detailed description of the technique, see reference 5.

In all animals which received the higher doses, and in some with the lower amounts of enkephalins, we found signs of central excitation such as rubbing and licking, but in no case did the full picture of stereotypy develop, i.e. the stage of biting and gnawing was not reached. 3 h after application, all rats were quiet and somewhat depressed.

Thus even with these forms of topical application, the full effect of enkephalins on morphine receptors has not been unequivocally demonstrated. Apparently the survival of extrinsic enkephalins in cerebral tissue is not sufficiently prolonged to permit the long-lasting stimulation which is required by the animals to develop morphine-induced gnawing. The latter appears within 1–3 h after topical application of the alkaloid. Perhaps better results could be obtained with continuous infusion of enkephalins into the ventricles; however the material available was insufficient for this purpose.

Another possibility must also be considered, viz. that in the brain larger peptides, like the C-fragment of Bradbury et al.[7] are required to activate the opiate receptors efficiently.

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