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LECTURES

Peptide Steroid Interaction

1

CONTROL OF ADRENAL FUNCTION BY PRO-γ-MELANOTROPIN.

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Corticotorpin (ACTH) is banded by β-lipotropin at the C-terminus and pro-γ-melanotropin (pro-γ-MSH) at the N-terminus in its precursor molecule pro-opio (melano) cortin (POMC). Hypothalamic stimulation of the anterior pituitary corticotrope releases all three peptides simultaneously.
The physiological function of β-LPH and its C-terminally derived opiate peptide β-endorphin is unclear. Pro-γ-MSH however has been found to potentiate the ACTH induced adrenal corticosteroidogenesis with a commitant increase in RNA synthesis. Adrenal hypertrophy and hyperplasia had been postulated as a consequence of ACTH hypersecretion although direct neural influences have been proposed. Evidence now suggests that pro-γ-MSH could be involved in the growth of the adrenal. Although the form released from the anterior pituitary is inactive as an adrenal mitogen, peptides generated from the extreme N-terminal of the peptide which do not contain the γ-MSH sequence have been found to stimulate DNA synthesis in vitro and cell proliferation in vivo, the activating cleavage mechanism most probably being neurally influenced at the adrenal. More recent evidence would also indicate that pro-γ-MSH is also involved in the regeneration of the enucleated adrenal gland.

2

Potentiation of ACTH-induced adrenal sterioidogenesis by amino-terminal fragments (NTFs) of pro-opiomelanocortin(POMC)-structure activity relationships.

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We have purified and characterized the various forms of NTF from both the anterior and intermediate lobes of the rat pituitary. NTF_{1-74} is the major product of the anterior lobe while NTF_{1-74}, NTF_{1-49} and $Lys^{1}\gamma_{3}MSH$ (ie NTF_{50-74}) are produced by the intermediate lobe. Studies were undertaken to discover what structural elements determine the biological activity of NTF. A highly sensitive dispersed adrenal cell bioassay was used which routinely displayed ED_{50} values for corticosterone output of 15 to 40 pM and 2 to 5 pM for synthetic human $ACTH_{1-39}$ and $ACTH_{1-24}$ respectively. None of the N-terminal fragments had significant intrinsic steroidogenic activity. When NTF peptides were added to ACTH standard curves much greater potentiations were observed with $ACTH_{1-24}$ than with $ACTH_{1-39}$. The most significant effects were induced by NTF_{1-74} which reduced the ED_{50} approximately five-fold when added to the $ACTH_{1-24}$ curve at 100 pM concentrations. Potentiation could be more readily studied by incubating different concentrations of NTF at a concentration of $ACTH_{1-39}$ close to that required for half-maximal response. Up to five-fold potentiations were obtained with ED_{50} values of less than 100pM for NTF_{1-74} and 100 to 4000pM for $Lys^{1}\gamma_{3}MSH$. NTF_{1-49} was found to have no potentiating activity. Our preliminary conclusion is that the most glycosylated form of NTF_{1-74} gives the greatest potentiating effects. Our previous findings have indicated that the extent of glycosylation profoundly influences the biosynthesic processing of NTF. This post-translational modification may may also affect biological activity.

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