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ACTH Signal Transfer to Mitochondrial Cholesterol Side Chain Cleavage in Adrenal Cortex

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The conversion of cholesterol to pregnenolone by adrenocortical mitochondria is the rate-limiting step in steroidogenesis. This process is stimulated dramatically by the action of ACTH through the sequential reactions, in which adenyl cyclase, cAMP-dependent protein kinase, cholesterol esterase and ribosomal protein synthesis are all involved. The de novo synthesized protein, the so-called labile protein with a half-life of approximately 10 min, is believed to stimulate the cholesterol side chain cleavage reaction by an unknown mechanism. Available evidences indicate that the electron transfer reaction from NADPH to $P\text{-}450_{scc}$ is mediated rapidly by adrenodoxin reductase and $P\text{-}450_{scc}$. In addition, these redox components are inactivated slowly with a half-life of 3.5 days after hypophysectomy. It is known that the corticoid output from adrenocortical cells starts within 5 min and reaches the maximum after 10 to 15 min of ACTH administration to animals. One can assume that under normal physiological conditions, both O_2 and NADPH are not limiting. Additionally, mitochondrial inner membranes are poor in cholesterol. In this context, the availability of substrate cholesterol to $P\text{-}450_{scc}$ is the most likely candidate for the regulatory mechanism.

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PEPTIDE-CORTICOID INTERACTIONS IN THE CENTRAL NERVOUS SYSTEM AND THE PITUITARY.

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The brain is an important target site for peripheral adrenal steroids (AS) which affect via specific binding sites and complex neurobiological actions both behavior and neuroendocrine functions. Recent new in vivo and in vitro autoradiographic approaches on brain sections allowed us to visualize these binding sites primary concentrated in limbic structures and hypothalamus of both rat and human brains. These data confirm the heterogeneity of central AS receptor systems. Among the various ways how AS may act in the brain is the possibility that they modulate peptidergic actions and/or interact with central neurotransmitter systems. Besides the effects of AS on vasopressin and CRF, we recently described a close interaction between AS and vasoactive intestinal peptide (VIP) both in the pituitary and the brain. Bilateral adrenalectomy (ADX) induced a decrease in VIP concentrations in the hippocampus and a marked increase in pituitary VIP levels. In the latter, glucocorticoids (GC) were shown to block VIP stimulation of prolactin release whereas the effect appeared more complex in the brain. On one hand, GC were shown to facilitate histamine-stimulated cAMP formation while suppressing both noradrenaline and VIP-dependent cAMP generation in the rat hippocampus. Besides, AS were shown to specifically interfere with VIP stimulation of serotonin ($5\text{-}HT_1$) binding sites in the hippocampal formation. The modulatory role of AS in VIP activity is complex since ADX not only masked some effects of the peptide, but may unmask some VIP actions which were not observed in normal animals. The present data may represent a neurobiological support for the behavioral effects of VIP, which involve a close interaction between the peptide, hippocampal 5-HT systems and AS.