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HORMONES, STRESS AND COGNITIVE FAILURE

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Corticosteroid hormones secreted by the adrenal after stress readily enter the brain. The hormones target in particular the hippocampus, a brain structure involved in learning, memory and mood. They exert long-term control over neuronal metabolism, excitability and structure through modulation of gene transcription. In this way corticosteroid hormones mediate the influence of environmental changes on the expression of genetic information in the nervous system. Numerous diseases have a genetic basis, but how the genes are regulated is not known. Corticosteroid hormones are extremely important in this respect and determine the context under which gene regulation occurs. Chronically too high or too low steroid levels increase vulnerability to a wide range of psychiatric, neurologic and inflammatory diseases (depression, fatigue syndrome, Alzheimers Disease), which are often characterized by depressed mood and cognitive failure. A fundamental question in stress research is, therefore, when stress hormones stop being essential for survival and become damaging to health. Why some individuals suffer from stress, while others under the same conditions do not, is another important question.
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THE MOLECULAR BASIS OF STEROID HORMONE BIOSYNTHESIS

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The first committed step in steroidogenesis is the conversion of cholesterol into pregnenolone, a reaction that takes place in mitochondria. This reaction is subject to acute control by tropic hormones that act through the intermediacy of cyclic AMP. The acute regulation is affected not by changes in cholesterol side-chain enzyme activity, but rather by increased access of substrate cholesterol to P450scc. A recently described mitochondrial protein, steroidogenic acute regulatory protein (StAR), appears to play a key role in the delivery of substrate to the inner mitochondrial membrane where P450scc resides. The evidence that StAR gene is mutated in subjects with congenital lipoid adrenal hyperplasia (lipoid CAH), the severest form of the congenital adrenal hyperplasias. The hallmark of lipoid CAH is a severe impairment in the ability to synthesize all adrenal and gonadal steroid hormones and the massive accumulation of cholesterol in the cytoplasm of the steroidogenic cells. Subjects die of complications of adrenal insufficiency if not treated with replacement hormones and genetic males are born as phenotypic females because of deficient testicular androgen synthesis in fetal life. The pathophysiology of the steroidogenic defects in lipoid CAH appears to include the metabolic defect in cholesterol movement to the inner

mitochondrial membrane and subsequent cellular damage resulting from cholesterol accumulation and cholesterol auto oxidation.

In human ovarian cells, tropic hormones increase StAR gene transcription through the action of cAMP. Expression of the StAR gene is promoted by the orphan nuclear transcription factor, steroidogenic factor-1 (SF-1), which acts on two distinct cis elements in the StAR gene promoter. SF-1 is required for cyclic AMP stimulated transcription of the StAR gene. It is of interest that the StAR gene is not expressed in the human placenta nor in choriocarcinoma cells. Thus, movement of cholesterol to the placental P450scc must occur by StAR-independent mechanisms. This accounts for the fact that pregnancies in which the fetus is affected with lipoid CAH are carried to term with no apparent deficiency in placental progesterone synthesis.

The exact mechanism of StAR action remains to be elucidated. However, structure/function studies have revealed the location of the important functional domains of the molecule. StAR is synthesized as a pre-protein with an N-terminal mitochondrial targeting sequence. However, this targeting sequence can be completely removed without affecting StAR function. In contrast, deletion of 10 or more amino acids from the C-terminus inactivates the protein. Moreover, the analysis of more than 40 patients with lipoid CAH indicates that all amino acid replacements causing the disease are located in the C-terminus. Collectively, these findings indicate that StAR does not need to enter into mitochondria to function and that the essential domains of the molecule related to the activation of steroidogenesis are in the C-terminus. Mitochondrial import may, therefore, be a mechanism to terminate StAR action.

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HEREGULIN AS A MARKER FOR BREAST CANCER TUMOR PROGRESSION.

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The growth of cancer cells depends in general on the activation of receptors by the binding of specific growth factors and/or the transmission of signals to the effectors responsible for proliferation. The erbB-2 oncogene product is a tyrosine kinase receptor that shares common structural features with members of the EGFR-like receptor family. Two additional members of this receptor family have recently been identified, the erbB-3 and erbB-4 receptors. Overexpression of the erbB-2 proto-oncogene is a negative prognostic factor expressed in high levels in nearly 30% of human breast cancer patients. The expression and function of erbB-3 and erbB-4 in breast cancer is yet unknown.

We have identified, characterized and cloned a growth factor, gp30, that activates the erbB-2 receptor. We purified and sequenced the gp30 protein. Using PCR, we then cloned its specific cDNA, which proved to be highly homologous to the recently cloned Heregulin. Our studies have demonstrated that relatively low concentrations of Heregulin induce differentiation of cells overexpressing the erb-2/4 receptors. We have recently shown that Heregulin activates erbB-3 and erbB-4 directly, and activates erbB-2 indirectly. The binding affinity of Heregulin for erbB-3 and erbB-4 is influenced by the number of erbB-2 receptors present, suggesting a "complex heterodimerization pathway".

The understanding of the mechanism by which this phenomenon occurs is critical for the development of novel therapies. There is now evidence for reciprocal regulation of the steroid and erbB-2 pathways. For example, it has been previously shown that estradiol induces downregulation of erbB-2 receptor expression. In contrast, the anti-estrogen tamoxifen, induced up-

regulation of the erbB-2 receptor. We have also shown that regulation of the erbB-2 receptor by both estradiol and tamoxifen can be blocked by Heregulin. More significant is our finding that Heregulin induces down regulation of the ER expression and more importantly, disrupts the ER function. Consequently, I postulate that in the presence of an active growth factor receptor pathway, such as the erbB-2/4 receptor pathway, cells can bypass their "normal" estro-gen requirement and become hormonally independent and anti-estrogen resistant.

Our data suggest a close cross talk between the erbB-2/4 and the Estrogen Receptor pathway. This "novel" discovery has allowed us to explore the relationship between Heregulin expression and anti-estrogen (tamoxifen) resis-tance. I hypothesize that Heregulin acts as an anti-estrogen by blocking the estrogen receptor function, thereby playing a role in the production of the more aggressive (ER-) phenotype. It has previously been postulated that erbB-2 overexpression is correlated with the acquisition of drug resistance. It has also been shown that most ER+/erbB-2+ tumors, do not respond to Tamoxifen treatments and that determination of ER expression is not sufficient to predict the response to antiestrogens. We have recently shown, that the presence of Heregulin leads to Tamoxifen resistance, making it critical to determine the relationship between the erbB-2 receptor family, Heregulin and resistance to Tamoxifen in clinical samples.

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LA PORTADA

Eduardo Schaffino (1858-1935); **Iglesia de Santa Catalina (Córdoba), 1910.** Oleo sobre tela, 39,5 x 61,5 cm. Cortesía del Museo de Bellas Artes, Buenos Aires.

Para datos biográficos del autor, ver *Medicina (Buenos Aires)* 1989; 49: 386.