S 5-4

PROGESTERONE RECEPTORS MEDIATING NEGATIVE FEEDBACK: NEW AND FAST, OR OLD AND SLOW?

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In the hypothalamic-pituitary-gonadal axis, the negative feedback control of LH by progesterone (P) is likely exerted at the hypothalamic level via retardation of the gonadotropin-releasing hormone (GnRH) pulse generator, as well as through inhibition of pituitary gonadotropin responses to GnRH stimulation. The extent to which these homeostatic, inhibitory feedback actions are mediated by the intracellular progesterone receptor isoforms, PR_A and PR_B, remains unclear. In recent studies we have determined that P injections, but not allopregnanolone or dexamethasone, can suppress LH levels in the serum of both wild-type (WT) and progesterone receptor knockout (PRKO) mice, suggesting that some of the negative feedback actions of P may be exerted independently of PR_A and PR_B. Injections of the PR antagonist, RU486, were also found to be without effect on pulsatile LH secretion in female rats. To determine if P can inhibit GnRH release by direct actions on the GnRH neuron, we have examined the effects P on superfused GT1-7 cells. Exposure of cells to medium containing 10^{-7} P produced a rapid, 30% reduction in GnRH release from these cells. In parallel experiments, treatment of GT1-7 cells with P (10^{-9} to 10^{-7}) inhibited forskolin-stimulated cAMP accumulation, and this effect was prevented by cotreatment with pertussis toxin, but not RU486. Injection of antibodies to Gi blocked the P effect. RT-PCR analysis revealed the presence of mRNAs encoding both isoforms of the recently described membrane progesterone receptors, mPR and mPR (Zhu et al., PNAS 100(5):2237-42, 2003). Western blotting similarly revealed expression of these proteins in the GT1-7 cells. Treatment of GT1-7 cells with mPR siRNA blocked specific P binding to GT1-7 cell membranes and reversed the P inhibition of cAMP accumulation. In current studies we are developing a neuronal- and GnRH neuron-specific PR gene knockout mice to further pursue these issues in vivo. Our investigations thus far reveal that the negative feedback actions of P on GnRH release may include direct, rapid effects on the GnRH neuron that are mediated by membrane receptors. These findings may have important implications for understanding of physiological control of GnRH pulsatility under normal circumstances, and in conditions under which progesterone negative feedback actions may be attenuated, such as polycystic ovarian syndrome.

S 6-1

ENVIRONMENTAL RESOURCES AS PREDICTORS OF LONGEVITY OF CENTENARIANS

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The question of longevity or mortality has been addressed in many previous studies (Robine, Forette, Franceschi, & Allard, 1999; Robine, Kirkwood, & Allard, 2001; Robine, Vaupel, Jeune, & Allard, 1997; Smith, 1993), and a primary interest has been in predicting why some people lead a very long life, and others do not (Thomae, 1993). Longevity researchers have compared survivors in longitudinal studies with non-survivors, typically contrasting mortality at younger ages (Wolinsky, Johnson, & Stump, 1995). Studies have not been able to answer the question whether there are different mechanisms for survival in midlife or for "younger" old age when compared to survival mechanisms important in very late life. Furthermore, we do not know whether these environmental resources impact longevity differently for men and women, individuals of different ethnicity and levels of education. The purpose of this paper is to elucidate on the impact of a set of environmental behavioral resource factors on longevity for different age groups (i.e., 60s, 80s, and 100s) and whether these factors influence longevity differentially for gender, ethnicity, and education. Data was obtained from nine-one sexagenarians, 92 octogenarians, and 137 centenarians of the Georgia Centenarian Study on life events, personality, coping and psychosocial resources. Results indicated that activities of daily living, Stress, Fatigue, and cognitive coping were significant predictors of survivorship. No differential predictive patterns were obtained for individuals of different ages. However, gender and education played an important role moderating the prediction of survivorship.