Understanding estrogen feedback actions on the brain using transgenic mouse models

A.E. Herbison, R. Porteous, J. Clarkson and R.E. Campbell, Centre for Neuroendocrinology and Department of Physiology, University of Otago, Dunedin, New Zealand. (Introduced by Jon Curlewis)

Estrogen exerts critical feedback actions upon multiple neuronal networks within the brain. One of the most important targets for estrogen is the gonadotropin-releasing hormone (GnRH) neuronal network that controls pituitary gonadotropin secretion and, thus, fertility, in all mammalian species. However, the GnRH cell bodies exhibit a scattered topography within the basal forebrain and this has greatly hindered progress in understanding their biology. Recent transgenic approaches, targeting GnRH neurons with fluorescent and calcium-sensitive reporter molecules, have been of great benefit in characterizing the cellular and molecular characteristics of adult GnRH neurons *in situ*. Furthermore, mice with cell type-specific knockouts of selective receptors have been of great use in refining information obtained from earlier global knockout mice. In addition, exciting new transgenic approaches are now being used to define primary and higher-order inputs to GnRH neurons within the GnRH neuronal network. The use of these transgenic approaches allows us to define mechanisms of estrogen feedback regulation of GnRH neurons. Data from global and neuron-specific estrogen receptor (ER) mutant mice demonstrate that ERalpha-expressing neurons are critical for estrogen positive feedback. As GnRH neurons do not express ERalpha, estrogen feedback must occur through ERalpha-expressing neuronal afferents to GnRH neurons. Experiments using Cre-dependent Pseudorabies virus in GnRH-Cre transgenic mice to trace these afferents, indicate that ERalpha-expressing neurons innervating GnRH neurons are located predominantly in the periventricular preoptic area. On-going electrophysiological and imaging studies suggest that neurons expressing the newly discovered neuropeptide, kisspeptin, provide a critical estrogen-sensitive neuronal population regulating the activity of GnRH neurons.