Intracellular mechanisms that modulate sensitivity to hormone negative feedback: the regulation of prolactin during lactation

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During lactation, high plasma concentrations of the anterior pituitary hormone prolactin are essential for milk production by the mammary gland. Normally prolactin levels are controlled by a classical hormone negative feedback loop, with prolactin stimulating the tuberoinfundibular dopaminergic (TIDA) neurones of the hypothalamus to release dopamine, which then suppress prolactin secretion from the pituitary gland. However in lactation, the sucking stimulus reduces the sensitivity of the TIDA neurons to prolactin negative feedback and consequently high prolactin levels are observed. Whilst many studies have described this physiological response, the underlying cellular mechanisms have only recently been investigated. Prolactin receptors are expressed on TIDA neurones and during lactation there is no down-regulation of receptor expression. Prolactin receptor signal transduction in the TIDA neurones, like most cells, is mediated by Janus kinase 2 (Jak) and subsequent phosphorylation and nuclear translocation of Signal Transducers and Activators of Transcription (STAT) proteins, particularly STAT5. For example, in cyclic or ovariectomised female rats, prolactin injection causes nuclear translocation of STAT5 in the TIDA neurones, indicative of functional prolactin signalling. However in lactation this pathway is resistant to stimulation by prolactin. That is, following prolactin treatment of suckling rats, STAT5 does not translocate to the nucleus. One potential explanation for reduced STAT5 signalling in lactation is upregulation of an inhibitor of Jak/STAT signalling and the most likely candidates are the Suppressors of Cytokine Signalling (SOCS) proteins. To date at least one member of this protein family, Cytokine Inducible SH2-domain-containing protein (CIS), has been found in all TIDA neurones and is upregulated by the sucking stimulus. Whether other SOCS family members or other regulators of Jak/STAT signalling are also involved remains to be determined. Clearly, the regulation of prolactin during lactation involves complex intracellular mechanisms that modulate sensitivity to a classical hormone negative feedback loop.