COMMENTARY ON: **30 years after: CNS actions of prolactin: Sources, mechanisms and physiological significance. BRIDGES RS, GRATTAN DR. *J Neuroendocrinol*. 2019; DOI: 10.1111/jne.12669.**

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Prolactin is a pituitary peptide hormone which, in addition to promoting milk synthesis, displays a myriad of seemingly unrelated pleiotropic functions exerted on many different cell types in both the periphery and the brain[1,2]. Circulating prolactin levels are regulated in a feedback mechanism by prolactin itself via its action on tuberoinfundibular dopaminergic (TIDA) neurons of the arcuate nucleus that subsequently release dopamine into the median eminence to tonically inhibit prolactin release by lactotrophs in the anterior pituitary[1,3]. During late pregnancy and lactation, prolactin secretion is disinhibited due to a phenotypic switch of TIDA neurons from dopaminergic to enkephalinergic, leading to high circulating prolactin levels[3]. In a paper published in the original volume of the Journal of Neuroendocrinology (1989), Rubin and Bridges showed that reproductive state-dependent changes in prolactin levels in the cerebrospinal fluid (CSF) correspond to alterations observed in circulating plasma levels (e.g. mirroring the increase in prolactin levels in lactating rats following suckling)[4]. This study prompted a series of questions with regards to the source of prolactin in the central nervous system (CNS), the existence of a prolactin transport system from the periphery to the brain, its neurochemical actions, and most importantly the physiological functions of prolactin in the brain. In addition to the state-dependent variations in CSF levels, early recognition of prolactin's role in maternal care was also indicative of central effects[5]. Advances over the past three decades in the understanding of the mechanisms underlying central effects of prolactin are summarized in a comprehensive review by Bridges and Grattan in the 30th Anniversary Special Issue of the Journal of Neuroendocrinology[6].

Extensive evidence indicates that peripheral prolactin is the major source of its central effects, however the contribution of endogenous brain prolactin remains controversial[6]. Early observations of state-dependent changes in CSF prolactin levels matching plasma levels[4] and high prolactin binding to the choroid plexus in brain ventricles[7] suggested the existence of a receptor-mediated transport system at the choroid plexus[8]. However, recent work by Brown and colleagues using radiolabelled prolactin demonstrated saturable transport into the brain of mice lacking prolactin receptor (PRLR)[9]. Based on this and other findings, Bridges and Grattan suggest that prolactin is not likely to enter the brain at the choroid plexus, but rather at the level of cerebral microvasculature, possibly via an unidentified carrier molecule. Interestingly, although the site of prolactin transport into the brain remains unknown, PRLR expression in the choroid plexus is physiologically important. PRLRs mediate differential transcriptional responses to prolactin during diestrus and lactation, and their expression is increased in the choroid plexus during lactation[10]. Notably, mRNA of the mitogenic polypeptide insulin-like growth factor 2 (IGF2) was recently shown to be dramatically increased in the choroid plexus during lactation in a PRLR-dependent manner, suggesting a possibility of neurogenesis associated with lactation at this site[10].

The distribution of PRLRs, as well as the cellular machinery underlying prolactin action in the brain, have been elucidated during the past 30 years. PRLR belongs to the class I cytokine receptor family and is expressed in various isoforms[11-14]. Early work led by Paul Kelly was instrumental in

the understanding of prolactin receptor biology, as well as the distribution of the various isoforms throughout the body. Signaling pathways downstream of PRLR have also been largely deciphered[15,16], and phosphorylation of the signal transducer and activator of transcription 5 (STAT5) upon prolactin binding to the long form of PRLR is now routinely used to assess genomic prolactin action in the brain[17]. Prolactin has also been shown to have rapid effects on subsets of hypothalamic neurons[18,19]. In particular, Augustine and colleagues recently reported that firing of oxytocin neurons from the rat supraoptic nucleus is differentially regulated by prolactin in virgin, pregnant, and lactating animals, likely impacting oxytocin secretion in various reproductive states[19]. Strikingly, the same study found that, in contrast to a lack of effect on vasopressin neurons in virgin rats, prolactin, possibly via afferent inputs, inhibited vasopressin neuron firing in lactating rats, suggesting that it might be involved in the regulation of the body fluid during lactation[19].

Prolactin acts on various neuronal populations underpinned by widespread receptor expression in the brain. PRLR expression is most prominent in, but not limited to, medial periventricular hypothalamic nuclei. Recently, using a PRLR reporter mouse line, Kokay and colleagues provided a detailed map of the long PRLR isoform distribution in neuronal cell bodies and processes throughout the brain[20]. In line with the widespread distribution of PRLR, prolactin's function in the brain is complex with a multitude of behavioural and physiological consequences, some of which have been mentioned above[1,6]. Prolactin is an important mediator of maternal behaviour, and the medial preoptic area has been identified as the central hub of prolactin action, promoting a set of behaviours culminating in maternal foster care of the offspring[21,22]. Prolactin and placental lactogen also regulate appetite and food intake associated with pregnancy and lactation, in part by attenuating the leptin sensitivity of leptin-sensitive neurons of the arcuate and ventromedial nuclei[23,24]. The common feature of these biological functions is to enable maternal adaptation[1].

In conclusion, pivotal findings over the past 30 years have provided a better understanding of prolactin's ever-expanding set of physiological functions, with the promise of further progress in the future. Readers are urged to peruse Bridges and Grattan, 2019 for a comprehensive overview, as well as highlights, of the most important findings in the field[6].

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