Dopamine control of prolactin secretion

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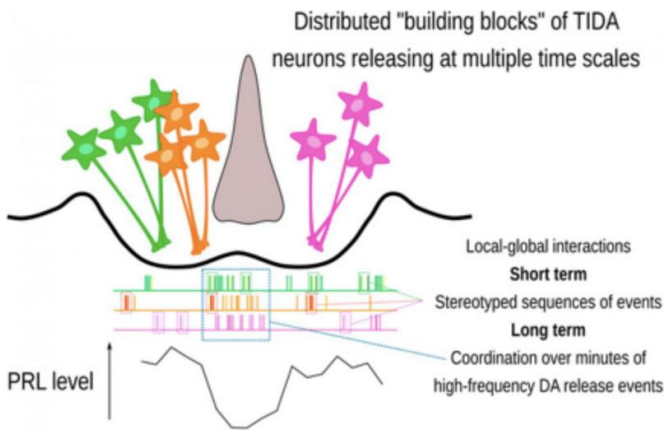

This figure shows how TIDA neurons release dopamine at the level of the median eminence. Credit: PLOS Blogs

In women, a major role of prolactin is to initiate and sustain pregnancy and lactation. During pregnancy, prolactin secretion from the pituitary gland is important for pregnancy maintenance and prolactin levels are correlated with miscarriage occurrence. When prolactin levels fail to increase properly, there is a higher risk of miscarriage1. But prolactin levels are also important during the female reproductive cycle – as increased prolactin secretion can cause infertility by inhibiting the release of hormones that trigger ovulation. So prolactin levels cannot be too high to allow ovulation and pregnancy to occur, but also have to increase at a proper rate during early pregnancy to ensure pregnancy success. But how the body carefully regulates prolactin in real time has been a mystery – until now.

Regulation of prolactin secretion

The body controls its hormonal release by means of positive and negative feedback. In a general way, hormones secreted in the hypothalamus (area of the brain that controls the body's homeostasis) stimulate the pituitary gland to secrete several hormones. These hormones enter the blood stream and act in peripheral target glands, stimulating further hormonal release (positive feedback). Subsequently, those hormones secreted by the target glands reach back to where the process started, suppressing hormonal secretion in both hypothalamus and pituitary (negative feedback). Like your home thermostat, sensing when your house is getting too warm, and turning on the air conditioner. Once the optimal temperature is reached, the air conditioner is turned back off.

But prolactin is different. It lacks a target peripheral gland, and therefore is not regulated through the standard negative feedback mechanisms that resemble your thermostat. Unlike other pituitary hormones that are stimulated by the hypothalamus, prolactin secretion is controlled by inhibitory dopaminergic inputs, produced in the tuberoinfundibular region of the hypothalamus (TIDA). We know that dopamine inhibits prolactin (and prolactin in turn, stimulates dopamine), but we do not know the temporal relationship among these players. The activity of dopaminergic neurons is very fast, firing in bursts of spikes happening at 20 seconds intervals2. Prolactin response, in turn, occurs in a much slower way. So how does all this rapid activity of dopaminergic neurons translate into dopamine release at the median eminence and subsequent (slower) prolactin secretion?

In a recent study published in *PNAS*, Romano and colleagues used an innovative new approach to investigate real time interaction between dopamine and prolactin. The researchers were able to measure dopaminergic release from TIDA neurons, correlating it to prolactin levels in freely moving mice, in real time, for several days! They implanted several miniaturized carbon fibers directly into the median eminence of female mice. This area is the part of the hypothalamus where the hormones are released, being the connection between brain and pituitary gland.

There is a hierarchical relationship between different dopaminergic neurons

By analyzing dopaminergic secretion over several days, the authors found that dopamine release was more frequent during the night, and that periods of intense dopaminergic activity were always followed by periods of silence. This makes sense within the feedback nature of the neuroendocrinology system, where hormones are released in pulses, to prevent down-regulation of target receptors. Elevated constant hormonal levels results in a decrease in the quantity of the hormone receptor, resulting in decreased sensitivity (down-regulation).

Analyzing dopaminergic currents on the basis of their shape, the authors realized that the dopaminergic neurons are stereotypically organized in distinct groups, with different and specific firing rates. These stereotypical features of the dopaminergic neurons were consistent between different animals and different days of recording. When dual-carbon fiber recordings were performed in two distinct dopaminergic neurons 500 ?m from each other, the authors discovered that dopaminergic firing events were coordinated within minutes during most of the recordings. Therefore, the activity from all those different TIDA groups is somehow coordinated over a range of minutes before dopaminergic release in the median eminence.

Novel integrated view of how dopamine controls prolactin secretion

Although all TIDA neurons release dopamine in the median eminence, there are different subsets of TIDA neurons, with similar firing patterns among the members of the same group, but not coordinated with other groups (those different TIDA groups are shown in the figure as green, orange, and magenta). Each one of those groups of TIDA neurons follows a stereotyped sequence of events. Meaning that locally, there is an organization of frequencies and the firing events occur as sequences (Short-term interaction). Those local dopaminergic patterns are fine-tuned within pre-established time windows, being totally integrated in the median eminence, before actual dopaminergic release (Long-term interaction).

This type of hierarchical organization of rhythmic activity has been previously seen in several other brain regions, and evolutionarily preserved among several species3. This repetitive rhythmic neural activity generates neural oscillations, which can vary in magnitude and/or frequency. In brain regions with hierarchical organization, several different neuronal oscillators form a linear progression, with slower oscillations regulating the amplitude (size) of the faster ones. This serves as a mechanism to transfer information from large-scale brain networks to the fast, and local cortical, integrating functional systems across multiple spatial and time scales.

This is the first time that a study has been capable to show that the median eminence is capable of integrating hierarchical neuronal oscillating networks, in a specific spatio-temporal pattern. This study opens a whole new path to investigate how hormonal rhythms can occur on multiple time-scales, ranging from minutes and days to seasons, helping to explain slow endocrine events such as reproduction, growth, metabolism, and stress.

More information: Alison J. Douglas. Baby on board: Do responses to stress in the maternal brain mediate adverse pregnancy outcome?, *Frontiers in Neuroendocrinology* (2010). DOI: 10.1016/j.yfrne.2010.05.002

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