Raphe Glucose-Sensing Serotonergic Neurons Stimulate KNDy Neurons to Enhance LH Pulses via Stimulatory Serotonin-2C Receptor in Female Rats and Goats

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Dysfunction of central serotonergic neurons is known to cause depressive disorders in humans, who often show reproductive and/or glucose metabolism disorders. Previous studies suggest that raphe serotonergic neurons may sense an increase in glucose availability to regulate glucose metabolism, but it is unclear whether serotonergic neurons sense and mediate energy status to regulate reproductive function. This study, therefore, examined whether dorsal raphe (DR) serotonergic neurons sense high glucose availability to upregulate reproductive function via activating hypothalamic arcuate (ARC) kisspeptin neurons (also known as KNDy neurons), a source of gonadotropin-releasing hormone (GnRH)/luteinizing hormone (LH) pulse generator, using female rats and goats. RNA-seq analysis and double *in situ* hybridization revealed that stimulatory serotonin-2C receptor (5HT2CR) was mainly expressed in the KNDy neurons in female rats. The administration of fluoxetine, a selective serotonin reuptake inhibitor, into the mediobasal hypothalamus (MBH), including the ARC, significantly blocked glucoprivic suppression of LH pulses and hyperglycemia in female rats treated with intravenous 2-deoxy-D-glucose (2DG) administration as an experimental model of malnutrition. A direct infusion of glucose into the DR significantly increased *in vivo* serotonin release in the MBH and partly restored LH pulses and hyperglycemia in the 2DG-treated female rats. Furthermore, using an electrophysiological technique recording multiple-unit activity (MUA) volleys, as an indicator of GnRH pulse generator activity, in the ARC of female goats showed that central administration of serotonin or a 5HT2CR agonist immediately evoked the MUA volley, and central 5HT2CR antagonism blocked the serotonin-induced facilitation of GnRH pulse generator activity in ovariectomized goats. These results suggest that DR serotonergic neurons sense high glucose availability to reduce gluconeogenesis and upregulate reproductive function by activating GnRH pulse generator activity in mammals.