ncRNAs in brain-body metabolic games

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The worldwide increasing rate of obesity and associated metabolic disorders has led to a growing demand of examination of causative factors which ultimately could lead to the development of treatments of pathologies related to disrupted energy balance. Energy homeostasis is achieved by a tightly regulated communication between central nervous system and peripheral organs. The hypothalamus is the most studied energy balance-associated region of the brain due to its direct involvement in both sensing the metabolic states and control of feeding and energy expenditure. The anatomical location and inter-connected cellular composition enable this small region of the brain to regulate the energy balance of the whole body. In particular the arcuate nucleus (Arc) within the hypothalamus is one of the core units with the location easily accessible for the peripheral hormonal and nutrient signals including leptin, ghrelin, insulin, amino-acids. Energy balance and food intake regulating cells within Arc nucleus comprise of: 1 – orexigenic AgRP "hunger" neurons and 2 – satiety neurons – POMC secreting neurons and recently discovered OxytocinR-vglut2 neurons. AgRP neurons receive both homeostatic and "cognitive" signals and serve as monitoring and regulatory center for food intake. Here we show that disruption of microRNAs biogenesis (the Dicer gene conditional/inducible knock-out in mice) within the arcuate neurons leads to development of the hyperphagic obesity. Titration of the mutation allowed us to precisely control a level of the obesity phenotype. The described phenotype in the Dicer/CaMKCreERT2 mice with voracious hyperphagia on the regular chow diet closely resembles a phenotype of patients with Prader-Willi syndrome (PWS). This human genetic disorder similarly causes severe obesity and affected individuals suffer from hyperphagia and lack of satiation.