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Title

Hypothalamic regulation of glucose homeostasis: is the answer in the Matrix?

Authors

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Abstract

Neurons within the arcuate nucleus control energy balance and represent the functional substrates through which FGF1 deploys its anti-diabetic action. Alonge et al., (2020) now reports that the integrity of arcuate perineuronal nets, an extracellular matrix component that enmesh GABAergic neurons, is reversibly altered in diabetic rats, and a key component for FGF1-mediated diabetic remission. These novel insights unravel how perineuronal nets dynamically contribute to the central control of glycemia.

Main body (998)

The brain has emerged as a prominent player in the control of feeding behavior, energy expenditure and glucose homeostasis. The arcuate nucleus (ARC) of the hypothalamus contains highly specialized neuronal populations, including AgRP- and POMC-producing neurons, which represent the two main opposite branches of the melanocortin system (Morton et al., 2014). Several studies have consolidated the role of ARC neurons in the regulation of feeding behavior, metabolism and nutrient partitioning. Among these, recent reports have shown that a single intracerebroventricular (icv) injection of the fibroblast growth factor 1 (FGF1), a peptide produced in the brain by neurons, astrocytes and ependymal cells, leads to strikingly long-lasting normalization of blood glucose in a diabetic rodent model (Scarlett et al., 2016). The ARC and the median eminence (ME) were subsequently identified as primary targets for the anti-diabetic action of FGF1 (Brown et al., 2019). Taking advantage of various histological and molecular techniques in combination with *in vivo* metabolic analysis, [Alonge and colleagues \(2020\)](#) have now explored the role of perineuronal nets (PNNs) in FGF1-induced diabetic remission.

First described by Camillo Golgi more than a century ago, PNNs are specialized components of the condensed extracellular matrix that form honeycomb-like structures enmeshing the cell bodies of fast-spiking neurons, thereby controlling their activity and synaptic plasticity (Celio et al., 1998; Testa et al., 2019). The building blocks for PNN assembly, consisting of proteoglycans (PGs), chondroitin sulfate glycosaminoglycans (CS-GAGs) and PGs-interacting proteins, are provided by neurons, glial cells and cerebrospinal fluids to form a condensed mesh around neurons leaving space for the synaptic buttons of afferent synapses, and offering physical protection while structuring neurons plasticity and activity. PNNs-constituting GAG polysaccharides are composed of variable sequences of disaccharide units, and the tightness of the scaffolding structure surrounding neurons depends on both protein interactions and polysaccharide modifications. The appearance of PNNs coincides with the closure of the critical period during brain development and the integrity of PNNs has been involved in various brain functions and dysfunctions including memory storage, neurodegenerative and psychiatric disorders (Testa et al., 2019).

The study of [Alonge and colleagues \(2020\)](#) represents a converging point of several observations, mostly made by the same group. Indeed, the founding observation was that a single icv injection of FGF1 produced transient hypophagia and long-lasting (>3 weeks and up to 17 weeks) reduction in blood glucose levels in rodent models of type 2 diabetes (T2D) (Scarlett et al., 2016). Subsequent work reported that the postnatal formation of PNNs around ARC GABAergic neurons (mostly AgRP-neurons) and in the ME parallels the maturation of energy-sensing ARC neurocircuits in a leptin-dependent manner (Mirzadeh et al., 2019). In adults, the hypothalamic ARC/ME was therefore identified as a primary target for the anti-diabetic action of FGF1 (Brown et al., 2019).

Now, [Alonge and colleagues \(2020\)](#) (Alonge et al., 2020) reports a sharp decrease in the abundance of ARC PNNs in a hyperglycemic T2D rat model. Using a mass spectrometry technique, they highlight an imbalance in the sulfation patterns of CS disaccharide isomers toward an increased 4S/6S CS ratio that was associated with hyperglycemia in Zucker diabetic fatty (ZDF) rats compared to normoglycemic animals ([Figure 1A, B](#)), while central delivery of FGF1 resulted in a rapid (24 hrs) restoration of ARC PNNs abundance and sulfation patterns ([Figure 1B](#)). To gain insight into the function of ARC PNNs, the authors locally microinjected Chondroitinase ABC (ChABC), an enzyme which dissolves GAG into its disaccharide core units, in combination with icv FGF1 delivery in diabetic ZDF rats. While the targeted disruption of the components of ARC PNNs did not affect the anorectic responses associated with the central action of FGF1, it selectively surfeits diabetic remission. Indeed, unlike vehicle-treated diabetic rats, animals treated with ChABC experienced a transient decrease in blood glucose which rapidly returned to diabetic hyperglycemia levels. Thus, these results reveal that the integrity of ARC PNNs is necessary for the central action of FGF1 in eliciting a sustained, feeding-independent, diabetes remission ([Figure 1B](#)).

Overall, these results introduce the structure of PNNs as a new cytological architecture critically involved in the central control of energy balance and offer a yet unappreciated target for anti-diabetic strategies. However, some question remains. For instance, local ChABC application would disrupt the whole ARC PNNs cyto-structure, thereby limiting the identification of precise neural substrates. Similarly, while the PNNs/AgRP-neurons assembly seems a reasonable target for mediating the action of FGF1, it is likely that other ARC GABAergic neurons may participate in the long-lasting regulation of blood glucose and so far, no clear molecular mechanisms connecting PNNs and ARC neurons have been identified. By the same token, ME tanycytes are gatekeepers for the entry of metabolic signals and their action on ARC neurons (Prevot et al., 2018), and they strongly respond to FGF1 (Brown et al., 2019). Hence, it is tempting to speculate that the integrity of PNNs is required for tanycytes-neurons communication within the ARC/ME microenvironment, allowing for an optimized regulation of hypothalamic circuits by circulating hunger and satiety signals.

Given the role of PNNs in the maturation of hypothalamic networks (Mirzadeh et al., 2019), one would expect that any genetic or pathophysiological alteration of PNNs during development will increase the susceptibility for metabolic disorders in adulthood. Interestingly, genetic variants in the semaphorin 3A signaling pathway have recently been associated with an impaired development of hypothalamic melanocortin circuits and obesity in humans (van der Klaauw et al., 2019). As member of the chemorepulsive molecules family, semaphorin 3A is a well-known regulator of the function of PNNs (de Winter et al., 2016; Testa et al., 2019) and, as such, could represent an interesting molecular link between ARC PNNs formation and the central control of energy homeostasis.

In conclusion, [Alonge and colleagues \(2020\)](#) unveil a role for PNNs in the central regulation of glucose homeostasis. Further studies are warranted to precisely ascertain the role of PNNs in the development and functions of hypothalamic metabolic circuits together with the physiological

mechanisms by which ARC PNNs/neurons regulate peripheral organ activity in promoting sustained diabetic remission. Unraveling how individual components of PNNs participate in energy homeostasis may ultimately lead to novel and effective strategies against metabolic disorders.

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Declaration of interest

"The authors declare no competing interests"

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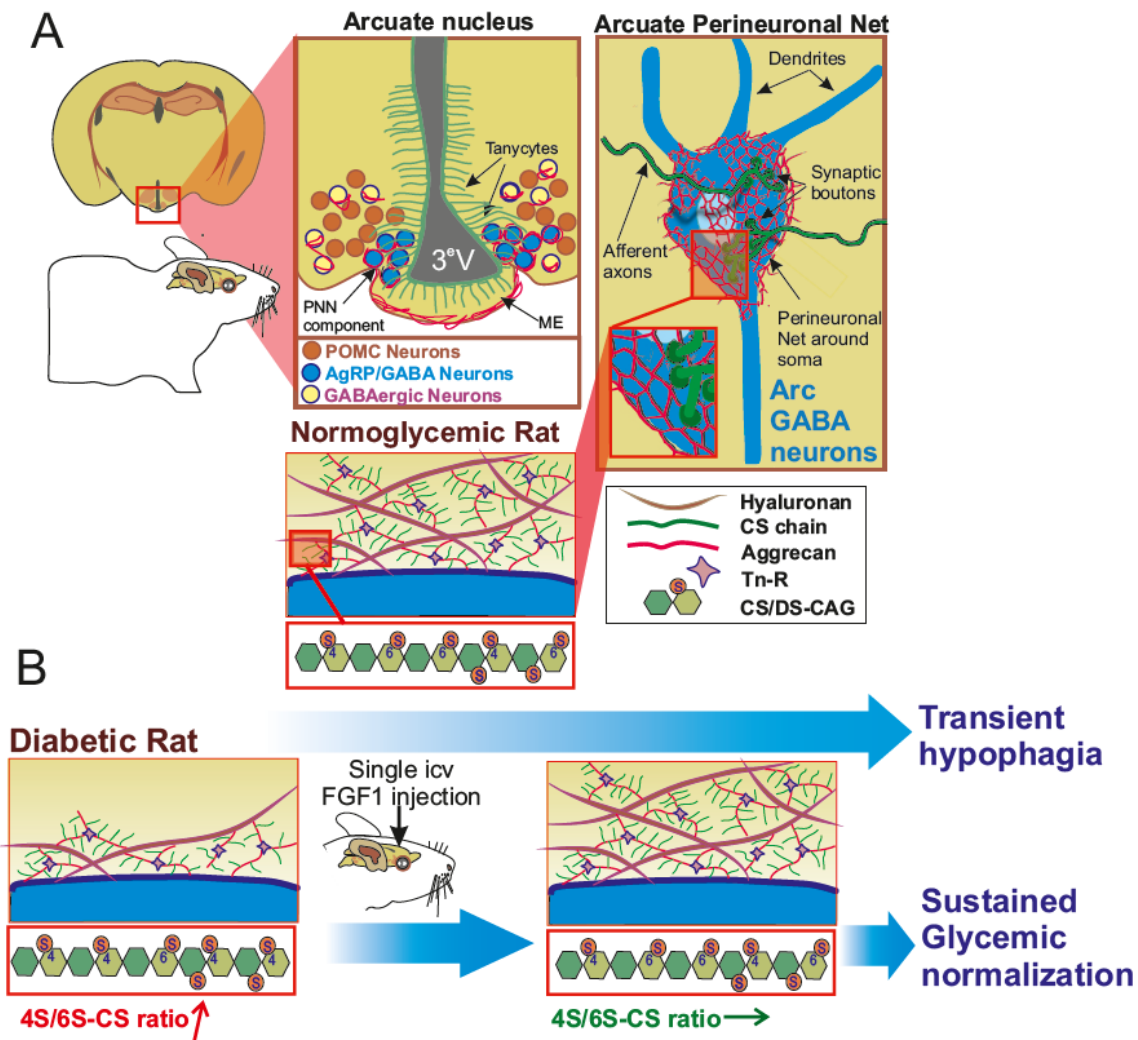


FIGURE LEGEND

The integrity of arcuate perineuronal nets (PNNs) is essential for the control of glucose homeostasis. (A) Arcuate perineuronal nets (PNNs) enmesh GABAergic neurons, among which include AgRP-expressing neurons, and form a functional continuum with the median eminence (ME). Core components of PNNs are hyaluronan, chondroitin sulfate (CS) CS- and dermatan sulfate (DS)-GAG glycosaminoglycan isomers (CS/DS-GAGs) and proteins interacting with proteoglycans or GAGs, such as aggrecan and tenascin (Tn-R). (B) In diabetic-hyperglycemic ZDF rats, the abundance of ARC PNNs is decreased and the proportion of disaccharides bearing sulfation in position 4 increase over that bearing sulfation in position 6 (4S/6S-CS ratio). A single intracerebroventricular injection of FGF1 results in normalization of both abundance of PNNs and

corrected "sulfation code". The proper integrity of ARC PNNs is required for FGF1-mediated diabetic remission but is dispensable for the acute hypophagic response.