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Short Communication

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Astrocyte: A Potential Target for the Treatment of Anorexia Nervosa

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Without homeostatic control of feeding behavior, energy balance will be disturbed towards either energy surfeit or deficit, respectively, leading to obesity or wasting. Anorexia Nervosa (AN) is a disorder characterized with food restriction and weight loss[1,2] due to intense fear of gaining weight and a distorted perception of body weight. The individuals with anorexia believe they are fat and seek to prevent weight gain by restricting the amount of energy intake even when they are starvation. Anorexia and its associated disorders impose a huge burden to our society, so treating and reversing anorexia are of paramount importance. However, the underlying mechanisms of anorexia are poorly understood, and there is a lack of effective treatments.

The nervous system consists of two classes of cells, neurons and glia. Thus, it is important to define the integrative processes of neurons and glial cells in the brain regions that control food intake. It is well recognized that neurons play critical roles in controlling feeding behavior and appetite, while little is known about glial influences on feeding. Astrocytes, the most abundant glial cells in the brain, are closely associated with neuronal synapses to scale synaptic strength and modulate neural circuits,[3-9] as well as with cerebral blood vessels to adjust blood supply.[10,11] Emerging evidence demonstrates the functional role of astrocytes in complex behaviors.[12,13] Interestingly, in response to high-fat diet (HFD) feeding, astrocytes in the ARC proliferate and express functional receptors for leptin,[14] adipocyte-derived anorexigenic peptide.[15,16] These studies strongly suggest the involvement of astrocytes in the regulation of appetite.

In the hypothalamic arcuate nucleus, AgRP (Agouti-related peptide) neurons are necessary and sufficient to rapidly evoke food intake while POMC (Pro-opiomelanocortin) neurons inhibit feeding.[17,18] The electrical activities of the neurons are critical for them to regulate food intake.[17,18] Prior studies demonstrate that both of the two types of neurons in the ARC receive synaptic inputs,[19,20] and glutamatergic excitatory synaptic inputs are crucial for neuronal firing.[19] We thus propose that astrocytes in the ARC could serve as surveyors of hunger states and in turn modulate feeding by rewiring the appetite control circuits in the ARC. In anorexic mice, astrocytes may negatively regulate feeding by reducing synaptic strength at and the firing rate of orexigenic AgRP neuron through release of the inhibitory gliotransmitter(s), such as adenosine. Adenosine in turn inhibits synapse transmission and neuron firing rate by acting on A1 receptors in both pre- and post-synaptic neurons.[21-24] Collectively, we propose that glial cells may actively participate in regulating energy balance by modulating appetite control circuits. It is well recognized that hypothalamic arcuate nucleus is a key brain region that control energy intake and energy expenditure.[25-27] In our recent studies, we find that food intake is also under the control of astrocytes. For instance, we find that the food intake is reduced by selective chemogenetic activation of astrocytes localized in the mediobasal hypothalamus in mice.[28]

Collectively, these results indicate that glial cells may also, at least in part, contribute to the development of anorexia nervosa. Furthermore, emerging evidence indicates that appetite is also under the control of "higher level" brain structures, such as cortex and hip-

pocampus, well- recognized brain regions implicated in emotion and cognition.[29] For instance, lesion of ventral hippocampus reduces appetite, indicating that ventral hippocampus exerts tonic inhibition on food intake. To fully understand the control of food intake and seek effective clinical therapeutics to treat appetite disorders, such as anorexia nervosa, it is of importance to consider both neuronal and glial processes localized in multiple brain regions.

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