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Invited review article

Spinal dorsal horn astrocytes: New players in chronic itch

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ATF3, activating transcription factor 3; CNS, central nervous system; CV, conventional; GRP, gastrin-releasing peptide; GRPR, GRP receptor; GFAP, glial fibrillary acidic protein; JAK, Janus kinase; SDH, spinal dorsal horn; SPF, specific-pathogen-free; STAT3, signal transducer and activator of transcription 3; TLR4, toll-like receptor 4; TRPV1, transient receptor potential cation channel subfamily V member 1

ABSTRACT

Chronic itch is a debilitating symptom of inflammatory skin conditions, such as atopic dermatitis, and systemic diseases, for which existing treatment is largely ineffective. Recent studies have revealed the selective neuronal pathways that are involved in itch sensations; however, the mechanisms by which itch turns into a pathological chronic state are poorly understood. Recent advances in our understanding of the mechanisms producing chronic itch have been made by defining causal roles for astrocytes in the spinal dorsal horn in mouse models of chronic itch including atopic dermatitis. Understanding the key roles of astrocytes may provide us with exciting insights into the mechanisms for itch chronicity and lead to a previously unrecognized target for treating chronic itch.

Introduction

Itch (or pruritus) is an unpleasant sensation that elicits the desire or reflex to scratch and normally serves as a self-protection mechanism from harmful external agents such as parasites.[1,2] In general, scratching can transiently relieve such itching sensations. However, under pathological conditions such as skin diseases like atopic dermatitis, other systemic disorders, such as liver and kidney diseases or HIV/AIDS, as well as metabolic disorders, itch becomes more severe and chronic, which leads to excessive, repetitive scratching.[1,3–5] Such scratching causes skin lesions, which can worsen the itch sensation and lead to further scratching (the vicious itch–scratch cycle).[1,3] Chronic itch affects millions of individuals worldwide,[6] but identifying the optimal treatment for it is a major clinical challenge.

A rapidly growing body of literature has revealed the existence of itch-specific neuronal circuitry in the peripheral and central nervous system,[1,2,7,8] and it has been proposed that aberrant modification of itch signaling at the levels of primary afferents and the spinal dorsal horn (SDH) might be involved in pathological chronic itch. Despite such progress in our understanding of the neuronal basis for itch sensation, the mechanisms by which itch turns into a pathological chronic state are poorly understood. In this review, recent advances in our understanding of the mechanisms that underlie chronic itch are highlighted, with a specific focus on the role of astrocytes, a type of glial cell in the central nervous system (CNS).

Glial cells in the CNS

Rudolph Virchow, a German anatomist, first found non-neuronal cells in the CNS and called them “glia”, the Greek word

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for “glue”, in the mid-nineteenth century.[9] However, it has now become apparent that glia are much more than “glue”, but rather are active players having crucial roles in controlling neuronal functions.[10,11] Glial cells express a number of neurotransmitter receptors for receiving inputs from neighboring cells including neurons and also a number of biologically active substances for giving signals to the cells. Glial cells are mainly classified into three groups: astrocytes, oligodendrocytes and microglia. The former two cell-types are derived from neural stem cells,[12] whereas microglia originate from precursor cells in the yolk sac during early embryonic development.[13,14] In the CNS, astrocytes are the most abundant population. Based on their morphology and location, rodent astrocytes have been classified into two groups, protoplasmic astrocytes in the grey matter and fibrous astrocytes in the white matter.[15] Protoplasmic astrocytes ensheath synapses and are in contact with blood vessels, and fibrous astrocytes are in contact with the nodes of Ranvier.[15] However, recent studies have indicated a diverse cell population, with distinct properties in different brain regions.[16,17] Astrocytes occupy nonoverlapping spatial territories, and their processes are intimately associated with synapses.[15,18] The processes of one astrocyte are known to contact tens of thousands of synapses at a structure termed the tripartite synapse to recognize the structural and functional relationship between the astrocyte and the pre- and postsynaptic terminals.[18,19] Astrocytes do not produce action potentials, but they do increase intracellular Ca^{2+} levels in response to neurotransmitters (glutamate, dopamine, noradrenalin, serotonin, ATP, etc.) via activation of their cognate receptors.[20,21] By responding to such extracellular stimuli, astrocytes evoke various cellular responses including production and release of gliotransmitters (ATP, D-serine, and glutamate) and trophic factors, which act on neurons and modulate synapse formation, maturation, efficacy, and plasticity.[15,20,22] A growing body of evidence using astrocyte-specific molecular and genetic manipulations has revealed that astrocytes play a pivotal role in neuronal function under physiological and pathological conditions.[15,17,20,22–25]

Reactive astrocytes in the SDH in models of chronic itch

Advances in the understanding of the mechanisms of acute and chronic itch have been achieved by the development of animal models. For chronic itch, several models have been established, most of which focus on cutaneous skin diseases, including atopic dermatitis, contact dermatitis and xerosis (dry skin).[8,26,27] Using the model of atopic dermatitis NC/Nga mice, an inbred strain of Japanese fancy mice that show spontaneous scratching behaviors when maintained under conventional (CV), but not specific-pathogen-free (SPF) conditions,[28] it was found that CV-NC/Nga mice have astrocytes with upregulated glial fibrillary acidic protein (GFAP), an astrocytic marker, in the SDH (Fig. 1).[29] Morphologically, the SDH astrocytes showed enlarged cell bodies and extensively arborized processes. These alterations are well-known histological criteria of reactive astrocytes.[30] Furthermore, reactive astrocytes in the SDH have also been reported in models of contact dermatitis[29] and dry skin.[31] Thus, reactive astrogliosis in the SDH occurs under chronic itch conditions.

Interestingly, astrocytic activation seems not to be induced in all SDH segments. Indeed, reactive astrocytes in the SDH are observed mainly in cervical and trigeminal segments that correspond to the nape of neck, rostral back, ear and face where the itchy mice have extensively scratched and skin lesions have developed.[29] In contrast, in the lumbar segments that do not corresponded with lesioned skin, GFAP expression is unchanged. Thus, reactive astrocytes may be restricted to the segments corresponding to the

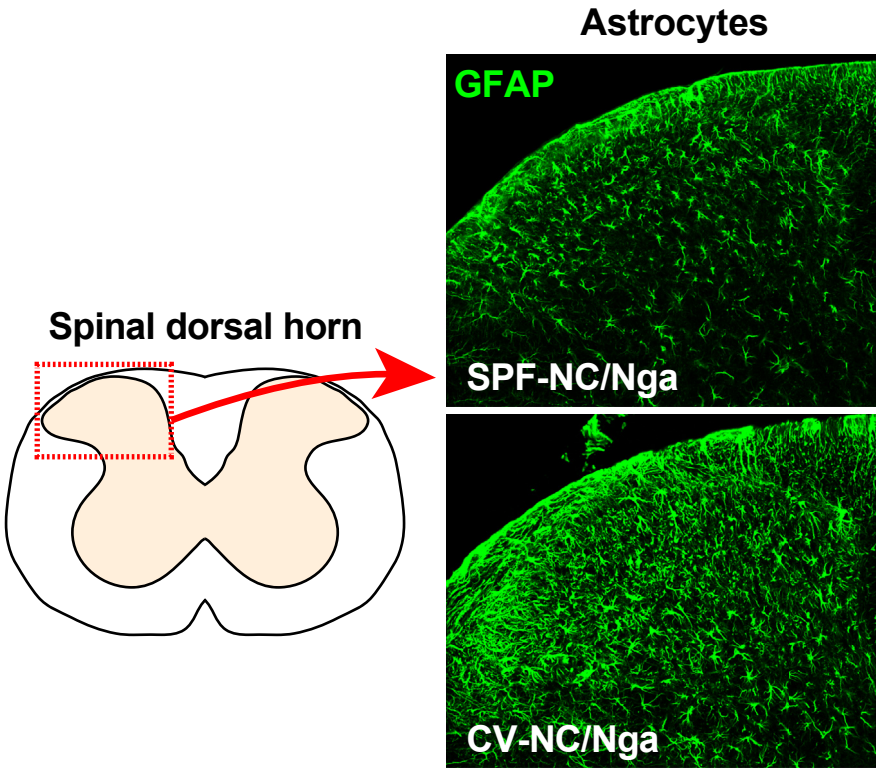

Fig. 1. Reactive astrocytes in the spinal dorsal horn in a model of atopic dermatitis. Immunofluorescence of the marker of astrocytes in the cervical spinal dorsal horn of SPF- and CV-NC/Nga mice. CV-NC/Nga mice have astrocytes with upregulated GFAP in the SDH. Morphologically, the SDH astrocytes showed enlarged cell bodies and extensively arborized processes.