Comment on: Differential effects of human fibromyalgia sera on murine satellite glial cells

Sirs,

We read with interest the fascinating report by Mercado *et al*. describing the acute activation of sensory ganglia cells in response to fibromyalgia (FM) sera (1). Consistent with emerging evidence supporting the role of satellite glial cells (SGCs) in chronic pain (2) and as the epicentre of fibromyalgia pain (1), they examined the response pattern of non-reactive glial cells to adenosine-triphosphate (ATP) (1). However, ATP-insensitive SGCs have not yet been characterised in the literature.

SGCs are present in various sensory ganglia, including the dorsal root ganglia (DRG), where the neuronal cell body is tightly surrounded by several metabolically active, immunocompetent SGCs. These cells facilitate SGC-neuron coupling and bidirectional calcium signalling (3, 4). SGC activation occurs via ATP released by ganglion neurons, which transmits signals through purinergic receptors (P2X7, P2Y2) on SGCs. Glutamate released from SGCs activates mGluR5 on neurons, contributing to these excitatory effects (5). Variable expression of purinergic receptors is a key factor in neuron-glia communication and pain signalling (6). Upregulation of these receptors on SGCs enhances ATP-mediated signalling, leading to increased levels of glutamate and pro-inflammatory cytokines, which promote neuronal excitability and contribute to chronic pain (7).

The study by Mercado *et al*. reports that the intracellular Ca2+ influx response of SGCs was observed in about a third of cells exposed to serum from healthy controls (HC), and in twice as many cells (32% more) when ATP was added. However, SGC activation is more prominent with FM serum alone in about half of the cells (45%), but with less additional activation (10% more) when ATP is added. Interestingly, while blood factor(s) from FM patients may cause SGC activation slightly higher than from HC (45% *vs*. 34%), this excitatory effect of human serum, when combined with ATP, had a modest impact in FM compared to controls (FM added 10% *vs*. 32% in HC). This intriguing phenomenon, that sera from FM patients interfere with ATP's excitatory effects on glial cells, remains poorly understood. Furthermore, downregulation or functional impairment of purinergic receptors on SGCs may provide a protective effect by reducing neuroinflammation and nociceptive transmission. Mercado's group hypothesised that a subset of SGCs is ATP-insensitive and acutely activated by FM serum. However, ATP-insensitive SGCs, which probably lack purinergic receptor expression, have not yet been characterised in the literature.

In their study, they included a 'painful' control group. A diagnosis of FM can be made when the widespread pain index (WPI) and symptom severity score (SSS) are sufficiently high (WPI ≥7 and SSS ≥5, or WPI 3–6 and SSS ≥9) (8). As shown in Table I, the pain visual analogue scale ranges from 22 to 56 on a 100 mm scale, the number of tender points varies around 3 ± 3, the WPI is 4 ± 4, and the SSS of 4 ± 2 indicate that controls with an SSS of 5 points and WPI of 7 or more already meet the criteria for fibromyalgia. Similarly, healthy controls with a Polysymptomatic Distress Scale (PSD) score of 8 ± 6 may include individuals with scores above 12 who definitely have FM. Given the small number of HC (n=6) in the study, these factors could significantly confound the results. Furthermore, cell culture conditions and the SGC isolation protocol are crucial factors. The coupling between DRG neurons and glia is likely disrupted in cell culture compared to examining the entire ganglion (9, 10). The study findings that FM serum alone induces murine SGCs but deactivates ATP-conditioned glial cells are conflicting and warrant further validation. However, it probably highlights the complexity of fibromyalgia nociplastic pathways, including neuron-glia interactions in DRG physiology.

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