Letters to the Editors

Reply to the comment on: Differential effects of human fibromyalgia sera on murine satellite glial cells

Sirs,

We thank Aamar & Aamar (1) for their insightful comments. Their major concern is that in our experiment, only half of the satellite glial cells (SGCs) respond to ATP at 10 μM. In contrast with the generalised view, a recent analysis of a collection of single-cell transcriptional profiling data from diverse laboratories showed that purinergic receptors are not abundantly expressed in SGCs as previously reported (2). Most expressed P2 receptors in SGCs were P2X, particularly P2X7, which was present in only about 25% of SGC. P2X7 is the least sensitive P2 receptor to ATP, with an EC50 >100 μM (3, 4). It is remarkable that almost no expression of P2Y receptors was detected, (data obtained from https://painseq.shinyapps.io/harmonized_painseq_v1/).

SGCs are a heterogeneous population with specialised roles in the immune response, lipid metabolism, glutamate turnover, or sensory processing (5). Therefore, a differentiated pattern of receptor expression is expected between SGCs populations, including P2X receptors. We suggest that the ATP-unresponsive SGCs in our culture conditions of isolated neurons and their surrounding SGCs might not express P2Y or P2X receptors. As part of the review process of our work, we ran a concentration-response curve of ATP, and according with the expected results, DRG neurons were far more sensitive to ATP than SGCs (EC50=0.1 μM and 6 μM, respectively; data not shown). Ten μM ATP is an adequate concentration to stimulate SGCs (almost twice the EC50), suggesting that the expression profile of P2R in our culture is similar to that observed in single-cell RNA sequencing. Our culture conditions of isolated neurons with the surrounding SGCs are different from the slice preparation where the high density of connexins between adjacent SGCs may amplify ATP response signals giving the appearance of more generalised SGCs P2 receptor expression.

In our study, cells were classified based on their response to serum or serum + ATP. In control serum, Ca entry in SGCs that responded only to serum was half (measured as the area under the curve) of that produced in the SGCs that responded to serum and ATP. On the other hand, FM serum increased Ca signal equally in both groups as shown in Figure 2 of our article (6). One possible explanation for this paradox is the existence of more than one agonist in the serum that triggers the upsurge of Ca concentrations in neurons and in SGCs (7). We recognise that our early findings require further validation and replication.

Regarding the 'painful control group', rather than a dichotomous diagnosis, fibromyalgia is a continuum of symptoms crossing the health-disease boundary. The eminent researcher Frederick Wolfe called this phenomenon 'fibromyalgianess' (8). Our control group was composed of real-world healthy women with 'some fibromyalgianess'. As can be seen in Table I of our study, all fibromyalgia clinimetric parameters were sharply higher in patients when compared to controls, attesting the clear difference between the two groups under study.

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