Abstract:
Microglia are the resident macrophage and immune cell of the brain and are critically involved in combating disease and assaults on the brain. Virtually all brain pathologies are accompanied by acidosis of the interstitial fluid, meaning that microglia are exposed to an acidic environment. However, little is known about how extracellular acidosis impacts on microglial function. The activity of microglia is tightly controlled by ‘on’ and ‘off’ signals, the presence or absence of which results in generation of distinct phenotypes in microglia. Activation of G protein coupled purinergic (P2Y) receptors triggers a number of distinct behaviours in microglia, including activation, migration, and phagocytosis. Using pharmacological tools and fluorescence imaging of the murine cerebellar microglia cell line C8B4, we show that extracellular acidosis interferes with P2Y receptor-mediated Ca(2+) signalling in these cells. Distinct P2Y receptors give rise to signature intracellular Ca(2+) signals, and Ca(2+) release from stores and Ca(2+) influx are differentially affected by acidic conditions: Ca(2+) release is virtually unaffected, whereas Ca(2+) influx, mediated at least in part by store-operated Ca(2+) channels, is profoundly inhibited. Furthermore, p2y1 and p2y6-mediated stimulation of migration is inhibited under conditions of extracellular acidosis, whereas basal migration independent of P2Y receptor activation is not.
Taken together, our results demonstrate that an acidic microenvironment impacts on P2Y receptor-mediated Ca(2+) signalling, thereby influencing microglial responses and responsiveness to extracellular signals. This may result in altered behaviour of microglia under pathological conditions compared with microglial responses in healthy tissue.