PERSPECTIVES

Chemokines and HIV-1 virus: opposing players in Cajal–Retzius cell function

Marco Capogna
MRC Anatomical Neuropharmacology Unit, Department of Pharmacology, University of Oxford, Oxford OX1 3TH, UK

Email: marco.capogna@pharm.ox.ac.uk

Cajal–Retzius (CR) cells are early generated neurons that play a critical role for the maturation of cortical circuits (Soriano & Del Rio, 2005). These cells were discovered almost simultaneously by S. Ramon y Cajal and G. Retzius more than a century ago, but they still continue to fascinate neuroscientists. While their numbers progressively decline during development to an almost complete disappearance in the adult neocortex, this process is much less pronounced in the hippocampus, suggesting that in this structure they also play functional roles later in life.

The morphology of CR cells is reminiscent of a tadpole. In the CA1 region of the hippocampus, the soma and dendrites of CR cells are located in the stratum lacunosum-moleculare (SLM), whereas their axon can also span to the dentate gyrus (Marchionni *et al.* 2010). The SLM is an area of integration, receiving several extrinsic inputs and containing various GABAergic cell types that appear to gate the incoming information (Capogna, 2011). An important advance in hippocampal CR physiology was the discovery that they spontaneously generate action potentials (Mienville, 1998), suggesting a tonic influence on their cellular targets. This raises an important question: how is the intrinsic excitability of CR cells regulated? The main synaptic input to adult CR cells comes from GABAergic cells, whereas glutamate receptors are expressed at unusually low level in these cells (Marchionni *et al.* 2010). In contrast to most neurons, GABAergic responses remain excitatory in CR cells because they do not express the KCC2 transporter (Pozas *et al.* 2008), which is critical for the developmental switch from $GABA_A$ receptor-mediated excitation to inhibition.

Modulation of the synaptic $GABA_A$ receptor would certainly affect CR cell excitability. Interestingly, in this issue of *The Journal of Physiology*, G. Maccaferri and his group (Marchionni *et al.* 2012) discovered a more subtle and unexpected way to modulate CR cell firing, namely via a class of molecules called chemokines. These are cell-secreted proteins acting on G protein-coupled receptors. They act in the brain as a unique signalling system along with classical neurotransmitters and peptides. CR cells, in particular, express the chemokine CXCR4 receptor, whose physiological ligand is a molecule called CXCL12. Previous work of Maccaferri's group had shown that CXCL12 powerfully inhibits the spontaneous firing of CR cells (Marchionni *et al.* 2010). Importantly, Marchionni *et al.* now identify the molecular mechanisms underlying this action.

Marchionni *et al.* used CXCR4-EGFP mice to facilitate the identification of CR cells and monitored their spontaneous activity in acute hippocampal slices. They report that CXCL12 hyperpolarises the membrane and inhibits the spontaneous firing of CR cells by increasing the intracellular calcium concentration and opening a BK-type calcium-activated potassium conductance. This action appears to be independent of the activity of classical transmitters, because it also occurs when a cocktail of glutamatergic and GABAergic receptor blockers are co-applied.

Next, they tested HIV-1-related molecules as the CXCR4 receptor is also a co-receptor for the HIV-1 virus (Feng *et al.* 1996). Indeed, the HIV-1 envelope glycoprotein, gp120, can act as a functional agonist for the CXCR4 receptor (Bodner *et al.* 2003). Surprisingly, they observe that gp120 depolarises the membrane and increases the firing of CR cells. They convincingly show that this effect is also mediated by the CXCR4 receptor. Furthermore, they report that the gp120-dependent enhancement of spontaneous activity requires an increase in intracellular calcium concentration and the activation of calcium-sensitive chloride channels.

The results of this study are very stimulating and open new avenues in the understanding of the physiological and pathophysiological roles of CR cells. How can activation of the same receptor lead to opposite effects mediated by the same intracellular pathway and via different ionic mechanisms? The authors are well aware of this apparent paradox and propose some fascinating and perhaps not mutually exclusive scenarios. One is that CXCL12 and gp120 possess different intrinsic efficacy for the CXCR4 receptor that leads to different concentrations of calcium. Another possibility is that the agonists act on spatially segregated calcium pools linked to different effectors. Finally, the two agonists may also activate other second messenger systems and/or different G protein subtypes. From a pathological perspective, this study is also captivating because it proposes that CR cells are a target of HIV-1 virus-mediated damage to the brain. Therefore, an action on CR cells may contribute to some of the cognitive deficits of HIV-1/AIDS.

In the future it would be interesting to monitor intracellular calcium levels triggered by CXCL12 and gp120 using calcium imaging in CR cells. It would also be important to determine the subcellular localisation of the calcium-dependent BK and chloride channels on the plasma membrane of CR cells. This should clarify whether these effectors are spatially segregated or not.

In spite of the progress provided by Marchionni *et al.* (2012), many intriguing questions about CR cell function remain. Since CR cells mainly receive GABAergic inputs, it is crucial to know which interneuron types contact them. Are they local interneurons, such as neurogliaform cells, or interneurons whose somata are located in other hippocampal layers, such as oriens-lacunosum moleculare cells? What is the function of the spontaneous firing of CR cells? Does it contribute to the integration of CR cells into developing circuits, as occurs for cortical interneurons (De Marco Garcia *et al.* 2011) or does it trigger the secretion of reelin? Which neurotransmitter is released by CR cells? What is the computational role of these cells in the adult hippocampus? Answers to these questions will shed more light on the function of this still too enigmatic neuronal type.

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