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Newborn neuroblasts feel the field in the adult brain

Sisi Chen & David V. Schaffer

In the adult mammalian brain, new neurons are continuously generated from a small supply of neural stem cells in two regions—the dentate gyrus of the hippocampus and the subventricular zone (SVZ)—in a manner that modulates numerous learning and memory processes. In the latter region, immature neuroblasts must traverse millimetres of cortical tissue to reach their final destination in the olfactory bulb [1]. How do these cells navigate along this route, termed the 'rostral migratory stream' (RMS)? Our understanding is that RMS migration is guided by molecular and cellular mechanisms including chemoattractive and chemorepulsive factor gradients—some established with the aid of cerebrospinal fluid flow [1,2]. A new study published in this issue of EMBO *reports* raises the intriguing possibility that an endogenous electric field lying along the RMS might also be important in guiding directional cell migration [3].

In 1974, the development of the vibrating probe technique enabled highly sensitive measurements of small endogenous currents within living tissues to be taken [4]. The presence of electric currents and their associated direct current fields has since been established in a variety of adult and developing tissues. As one example, polarized ionic transport through Na^+/K^+-ATPases can establish a large potential difference (40–200 mV mm^{-1}) from the apical to basolateral surface of an epithelial cell layer, aided by the high ionic resistance of tight junctions. Furthermore, injury to such epithelial sheets triggers an electrical current that guides epithelial migration during subsequent wound closure [5].

Although electrophysiological investigations of neurons and their synaptic connections within the brain have been conducted for over a century, comparatively less is known about whether long distance, macroscopic electric fields are generated as a natural consequence of cellular membrane depolarization or currents. The work by Zhao and colleagues published in this issue presents, for the first time to our knowledge, evidence that endogenous electric currents exist along the RMS and that neuroblasts might migrate in the direction of the associated electric field, a process generally known as galvanotaxis.

By using the vibrating probe method, an endogenous electric potential gradient of 3.3 mV mm^{-1} was measured along the RMS; a separate determination based on current and resistance measurements arrived at a slightly smaller value of 2 mV mm^{-1}. As in the case of transepithelial potentials, this field might be generated by the spatial organization of Na^+/K^+-ATPases in the SVZ and olfactory bulb. Specifically, the authors found that epithelia lining the lateral ventricular wall, at the beginning of the RMS, had a high concentration of ATPases on the basal side, which might thus pump excess Na^+ ions into the brain. On the other end of the RMS, in the olfactory bulb, they found Na^+/K^+-ATPases primarily on the apical side of the epithelia, which might pump Na^+ ions outward from the olfactory bulb and thus create an ionic sink. The authors suggest that a resulting flow of Na^+ cations from the SVZ to the olfactory bulb is responsible for the low level direct current electrical field along the length of the RMS, which is supported by their finding that inhibition of the ATPase by ouabain significantly reduced the field strength.

In vitro and *in vivo* time-lapse data from this study and previous work [6] demonstrated that electric fields direct neural stem cell migration. Cao and colleagues found that high field strengths (>10 mV mm^{-1}) promoted clear and sustained directional migration towards the cathode. At lower strengths, closer to those measured between the SVZ and olfactory bulb (approximately 3.5 mV mm^{-1}), the *in vitro* migratory bias was slight yet statistically significant. Additionally, time-lapse analysis of labelled neuroblasts in live explant slices showed that migration towards the olfactory bulb was strongly enhanced by exogenous fields as low as 10 mV mm^{-1}—approximately three times the endogenous potential. Furthermore, reversing the field direction with a high exogenous potential (50 mV mm^{-1}) caused cells to steer off course and in the direction of the imposed field. Finally, by using pharmacological inhibition as well as RNA interference knockdown, Cao and colleagues implicate the P2Y1 purinergic receptor, which is expressed specifically in migrating neuroblasts, as a mediator of the galvanotaxis.

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The field of stem cell biology is increasingly recognizing the importance of not only biochemical but also biophysical regulatory cues, and this work provides further support for investigating the role of electrostatics in controlling cellular function. Naturally, it also raises several interesting and open questions. It is clear in this study that neuroblasts migrate in response to strong imposed electrical fields *in vitro* and *in vivo*, and weaker fields *in vitro*, although future work is necessary to establish definitively that the low electrical field measured *in vivo* (approximately 2–3.5 mV mm^{-1}) is sufficient to influence directional cell migration within the RMS.

In addition, these results raise interesting questions about possible relationships between electrostatic and biochemical

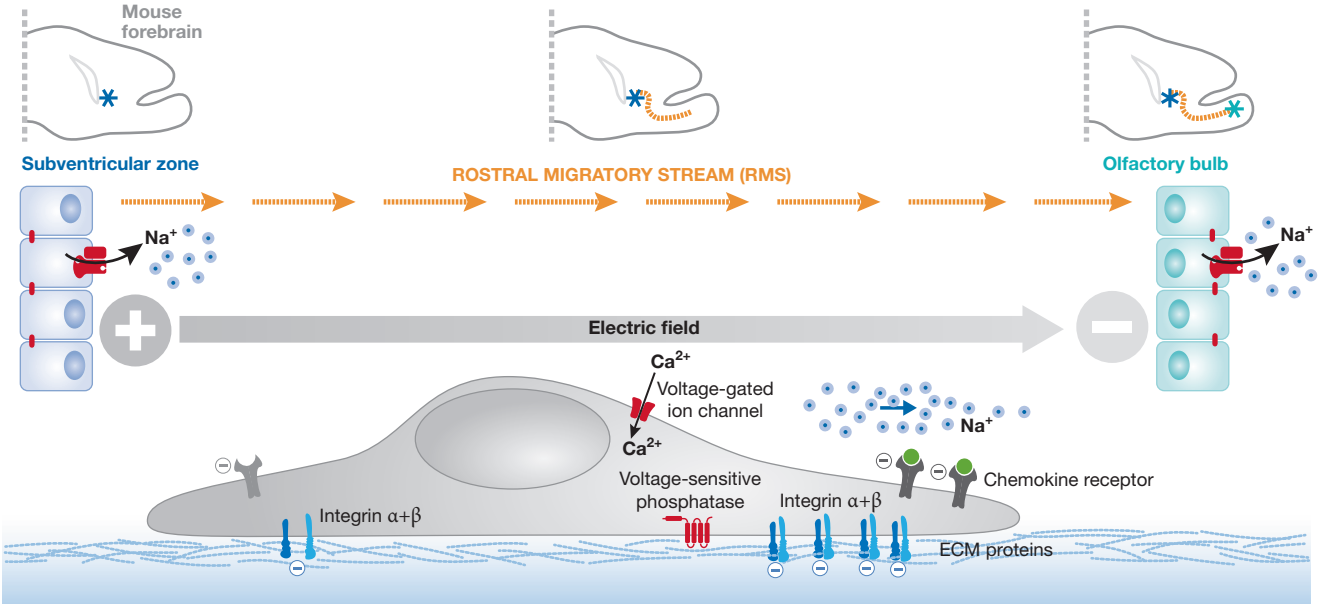

Fig 1 | There are numerous hypothesized mechanisms by which cells might sense an electrical field. A weak electrical field could impose a force on negatively charged cell surface receptors, or alternatively the electric force imposed on positive ions (Na^+) could result in the flow of their associated hydration shell, which exerts a drag force on cell surface membranes. The resulting asymmetrical redistribution of cell surface receptors, such as the ones involved in sensing chemokines or motogens, could affect cell migration. Alternatively, the electric field could conceivably trigger voltage-gated ion channels or exert forces on adhesion receptors, such as integrins, which result in asymmetrical binding to extracellular matrix (ECM) proteins. Finally, phosphatases, such as Ci-VSP or PTEN, mediate cellular responses to electric fields.

cues in regulating neuroblast migration. Such migration depends on gradients of the chemorepulsive factor Slit along the RMS [2], as well as the cell adhesion molecule PSA-NCAM, which enables cells to migrate as chains within the rodent RMS [7]. Investigating the relative importance of galvanotaxis compared with chemotaxis in guiding neuroblasts might benefit from inducible genetic manipulation of neural stem cells and their progeny *in situ* to establish further underlying molecular mechanisms. In addition, future work might address whether electric fields have any role in regulating neuroblasts that do not undergo RMS migration within the human brain [8].

Although the phenomenon of galvanotaxis in weak direct current fields is well established across cell types, and Cao and colleagues suggest a role for the P2Y1 receptor, in general the cellular and molecular mechanisms that underlie this process are not well understood. Many cells—including these SVZ neuroblasts—respond robustly to electrical fields of 10 mV mm^{-1} or more, yet these fields correspond to small potential differences (roughly 0.1 mV) across the dimensions of a cell [5]. One hypothesis is that small direct current fields drive ionic flow of free cations—namely Na^+—the hydration shell of which drags concordantly along charged membrane-associated proteins towards the anode (Fig 1). The result might be a cell surface gradient of key receptors that in turn direct migration. Another theory is that small potential differences may differentially bias voltage-gated ion channels, although the activation voltages for such gated channels typically range from 50–100 mV [5]. A third explanation is that electrical fields can generate forces on negatively charged cell surface adhesion molecules (such as integrins), leading to differences in cell–extracellular matrix interactions and migratory properties across the length of the cell [9]. Finally, the lipid phosphatase PTEN—a repressor of phosphatidylinositide 3-kinase signalling—mediates an electric field response during wound healing [10], and a structurally related phosphatase (Ci-VSP) that regulates the activity of phosphoinositide-sensitive ion channels was discovered to be voltage sensitive [11]. Given the established importance of PTEN in neural stem cells and glioblastomas, these factors might also offer potential mechanisms.

In summary, Cao and colleagues establish that electrical currents and field gradients exist along the RMS, provide further support for the observation that adult neuroblasts migrate directionally within electrical fields and provide evidence that an endogenous potential gradient along the RMS might help guide these immature neurons to the olfactory bulb. This study thus lays stimulating groundwork for future investigations to explore the roles of biophysical cues in guiding the fate and flow of stem cells and their progeny in the nervous system.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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