TRANSLATIONAL PERSPECTIVES

Translational perspectives: Interneurones start seizures

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As reported in The Journal of Physiology, Kandrás et al. (2019) have explored the respective roles of excitatory, principal cells and inhibitory interneurones with respect to initiating epileptiform synchrony in human neocortical tissue. In essence, they have re-addressed a long-standing question: are bursting cells initiating synchrony, or indeed inhibitory ones? This question appeared, at least in animal models and mesial structures, long-decided in favour of bursting principal cells (Traub & Wong, 1982; Wong et al. 1986). Some doubt was cast on this hypothesis in the case of human tissue because bursting could not be conclusively related to spiking, even though some neurones were able to generate induced bursts (Prince & Wong 1981, Avoli & Olivier 1989, Forching & Wyler, 1990). The merit of the study by Kandrás et al. (2019) is that they undertook the task to meticulously classify different types of discharges (spontaneous population activity, interictal spiking, seizure-like events), aiming to analyse their spatial and temporal spread, and also to relate this to the firing of putative interneurones vs. principal neurones (bursting or regular firing) in 86 brain slices from 30 patients with epilepsy, and in 26 brain slices from 19 tumour patients without. Obviously, they had to resort to human tissue in vitro, and also to artificial induction of epileptiform events using a disinhibition model (bicuculline), because seizure-like activity does not appear spontaneously in human brain slices.

What is physiological and what is epileptic?

Regarding interictal activity, the matter is more complicated. Initially, it was assumed to only rarely appear spontaneously (Schwartzkroin & Haglund 1986, McCormick 1989) and, if regularly so, then in human epileptic hippocampal or neocortical tissues (Köhling et al. 1998, 1999, Cohen et al. 2002). In subsequent studies, it was debated whether interictal activity had to be differentiated from spontaneous population activity, on the grounds that it also appeared in peritumoural tissue (Pallud et al. 2014) or, indeed, in tissue from patients not having displayed any seizures clinically at all (Tóth et al. 2018). Even though interictal spikes and spontaneous population events share characteristics such as increased power in high-frequency oscillations, as well as hub-like generation patterns (see below), it is thus possible that they constitute different entities because their durations and amplitudes are differently distributed: spontaneous events were defined as brief (<100 ms) and small (<50 µV) and interictal spikes were defined as longer (>150 ms) and larger (>100 µV). However, even the latter discrimination still leaves open the possibility that populations active during spontaneous events could be just subsets of those involved in interictal spikes. An important issue of the study by Kandrás et al. (2019) is that they bring further clarification in this matter: it is shown that there appears to be a qualitative difference between spontaneous population activities and interictal spiking because their single unit analyses demonstrate that different – and apparently mutually silent – neuronal populations participate in spontaneous population activities and interictal spikes, with more principal cells contributing to spontaneous population events, and more interneurones to interictal spikes. Because spontaneous population activity is more frequently found in epileptic tissue, there is, nevertheless, the open question of whether some relationship exists between either spontaneous population activity and interictal spiking.

Are interictal epileptiform events stereotypical?

The clear answer, perhaps not surprisingly, is ‘no’. Importantly, in tissue from therapy resistant patients, interictal spikes, similar to spontaneous population activity, could be generated hub-like, supra- or infragranularly, without spread into the other layers. Such laminar restrictions were also present in the case of seizure-like events, although they were not exclusive to tissue from patients with epilepsy. Interictal spikes thus appear to reflect the activity of synchrony-generating hubs, demonstrating that, under interictal conditions, there is probably a multitude of networks able to initiate synchronous discharges harbouring the propensity to trigger full blown seizures (Morgan & Soltesz, 2008). Hubs in this sense should be differentiated from hubs identified in imaging studies that refer to networks in different brain regions (Douw et al. 2015, Zubler et al. 2015), which obviously may co-exist.

What initiates the spikes: principal busters or interneurones?

This returns to the key question of the paper, which is hotly debated in the field. From the 1970s onward, textbook knowledge holds that seizures are initiated by over-excitation; indeed, in many textbooks, the classic figure of Ayala et al. (1973) is featured, showing a bursting neurone starting interictal spikes and seizure activity in the penicillin-focus model. Subsequently, an increase in intrinsic hippocampal neuronal bursting has been correlated with post-status epilepticus models in rodents (Chen et al. 2011), fast rhythmic neocortical bursting has been attributed to start spike-and-wave discharges in cats (Timofeev & Steriade 2004), pathologically interconnected bursting neurones were speculated to start hypersynchronous ictal-onset seizure activity in rodents (Li et al. 2019) and an increase in bursting propensity has been linked to peritumoural epileptogenic human tissue (Köhling et al. 2006). On the other hand, low-voltage fast...
ichonal onset activity in patients was shown to coincide with a reduction in the firing of large numbers of neurons recorded intracranially (Truccolo et al. 2011), along with preserved excitatory–inhibitory connections and sparse firing. An increase in firing and synchronization was again only seen in a different seizure type (i.e. spike-and-wave discharges (Truccolo et al. 2014). A decrease in hippocampal principal-neuron firing and an increase in interneurone firing at seizure onset were also reported in the pilocarpine model (Gras et al. 2013, Toyoda et al. 2015), indicating that a possible up-regulation of bursting (Chen et al. 2011) might not be crucial for seizure initiation. There are thus good indications that seizures, or at least those starting with low-voltage fast activity as the most common onset type, are initiated by GABAergic interneurones (de Curtis & Avoli, 2016). The present study by Kandracs et al. (2019) now gives additional decisive evidence: both during interictal spikes, as well as at seizure-like activity initiation, the relative majority of active cells was interneuronal in nature (~40–60%), with a 3–19% contribution of principal cells (and only a tiny proportion of ~2% bursting ones). This finding matches well with recent in vivo data obtained from patients with mesial temporal recordings (Ehalian et al. 2018); also here, interneuronal firing increased at seizure onset, along with principal neuronal firing only 10 s into the discharge. At least for this seizure type (spike and wave discharges and peritumoral activity may be an exception), we thus have to conclude that interneurones start the seizure – and not excitatory cells.

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