Epileptic rats as perfect models to understand epilepsy?

Epilepsy is a neurological disease that affects about 1% of the population in the world, most of them being children and teenagers. Animals suffering from epileptic seizures can also be found in several species (dogs, cats, chicken, monkeys). In particular, rats and mice with spontaneous seizures have been reported in several laboratories and their study has increased our understanding of the physiopathology of epilepsy. The GAERS model is probably the most emblematic example of the use of such animals in neuroscience.

The serendipity of GAERS

In the 80's, we observed, by chance, that rats from our local Wistar colony (Strasbourg, France), spontaneously displayed seizures with many features of absence epilepsy. This prototypical form of childhood epilepsy is characterized in human by recurrent 10-20 sec loss of contact (absence) concomitant with a specific electroencephalographic (EEG) activity called "spike-and-wave discharge" (SWD, Fig. 1). We first detected short spontaneous SWDs in about 30% of our rats, which were always associated with a typical "arrest" of their behavior. These SWDs were suppressed by antiepileptic drugs used in the clinic to stop absence seizures (e.g., valproate, ethosuccimide), whereas drugs known to aggravate these seizures in patients (e.g., phenytoine, carbamazepine), increased rats' seizures. When we bred rats with seizures, we rapidly obtained a lineage where all animals displayed SWDs and we decided to call it "Generalized Absence Epilepsy Rat from Strasbourg" or GAERS. Breeding brothers and sisters without SWDs also allowed us to develop the Non-Epileptic Control (NEC) strain.

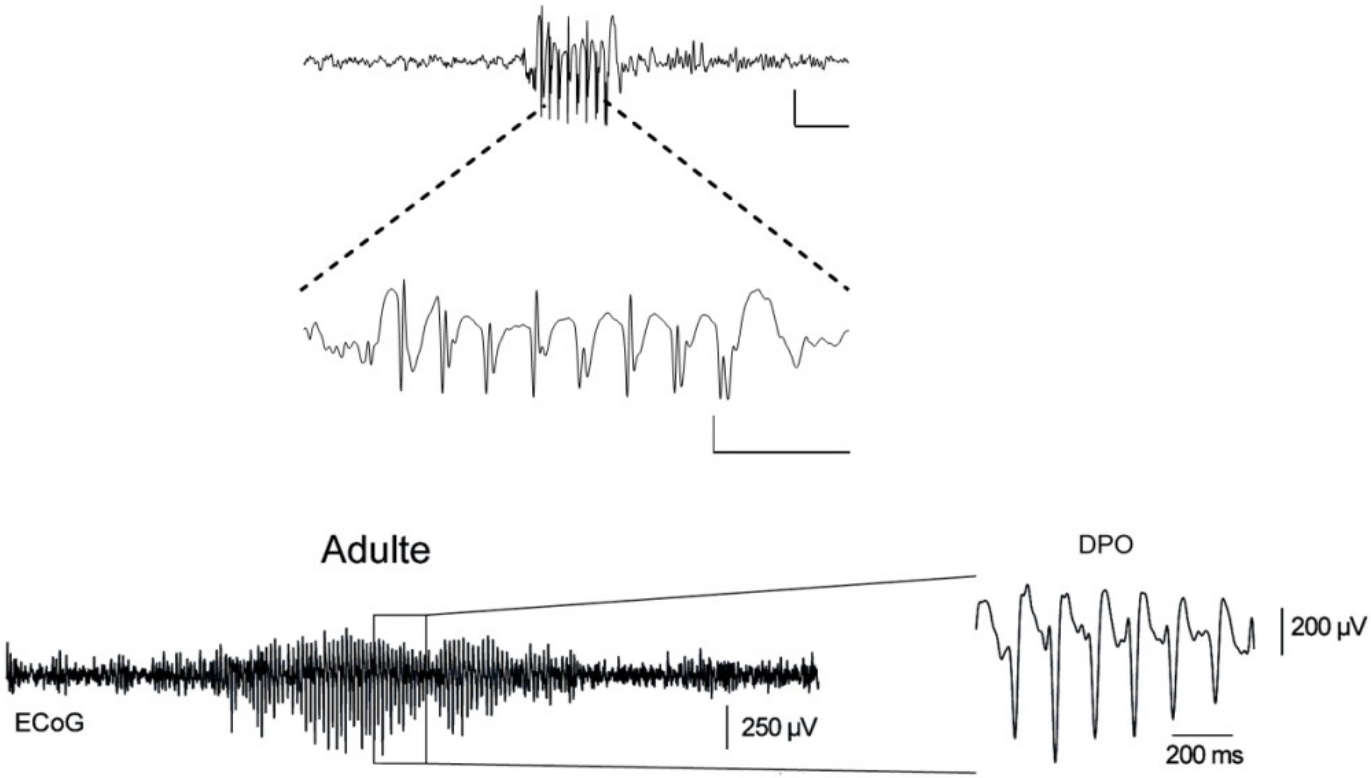

Fig. 1. TOP : Spike-and-wave discharges in GAERS (left side) are similar to discharges recorded by EEG in human patients with absence epilepsy (right side). BOTTOM : Spike-and-wave discharges in GAERS are suppressed by antiepileptic drugs that are used in the clinic to control absence epilepsy. Drugs that aggravate patients with this form of epilepsy increase seizures when given to GAERS.

The key role of the cortex in the initiation of absence seizures

The easiness to EEG record spontaneous SWDs in freely moving GAERS, first allowed us and others to understand that the cortex and the thalamus, two intimately connected brain structures, are the two main players in the generation of absence seizures, in line with human data. A decade ago we addressed the hypothesis that SWDs were initiated in a specific part of the cortex in GAERS by recording large population of neurons with multiple electrodes and appropriate signal analysis or functional magnetic resonance imaging (fMRI). We found that 90% of SWDs first occurred in the facial somatosensory cortex (SoCx), a region that integrate tactile information from the animal's face (Fig. 2) and rapidly spread (1-2 sec) to other cortices and thalamus. Occasionally, short SWDs occurred in SoCx without propagation to other brain regions whereas the reverse was never observed. Increase of blood flow was the highest in SoCx compared to other regions, when fMRI was performed, and inhibition of this structure by local drug applications or synchrotron-

generated microbeam irradiations, suppressed SWDs whereas inhibition of other cortical or thalamic structures was not effective.

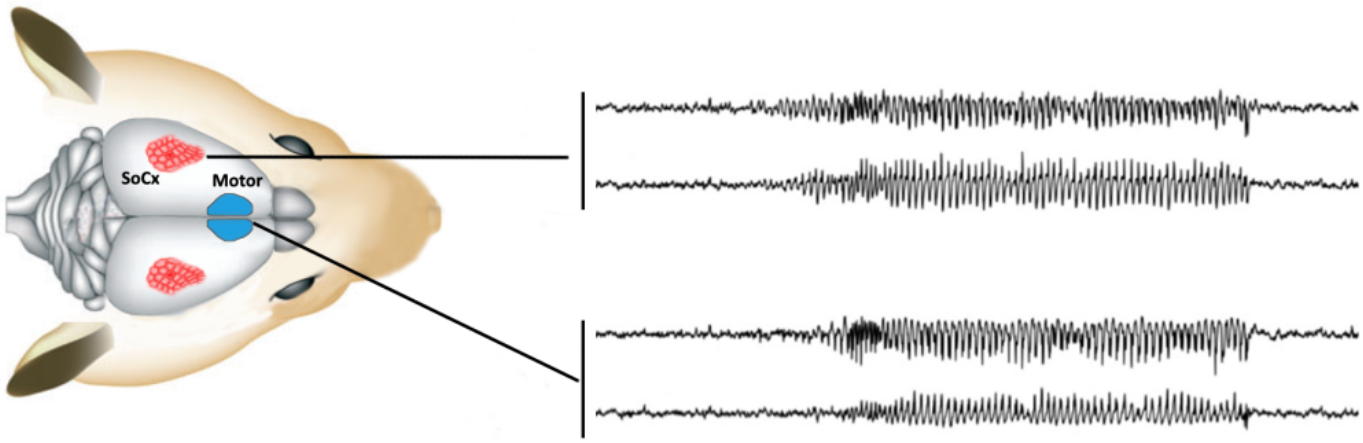

Fig. 2. EEG recording of a spike-and-wave discharge in GAERS in different brain areas (SoCx first two traces) and Motor cortex (last two traces). A delay of 1-2 sec occurred between SoCx and the other structures, suggesting a leading role of SoCx in the initiation of spike-and-wave discharges.

Absence seizures seen from inside the neurons

GAERS have allowed us to explore the cellular mechanism underlying SWDs by inserting a very thin electrode inside cortical and thalamic neurons to analyze on-line the subtle alterations, mainly at synaptic connections, that are responsible for the generation of SWDs. Using such intracellular recordings, we demonstrated that SoCx neurons are the first to change their activity by large and rhythmic synaptic excitations that generate nerve impulses. This repeated neuronal activity then propagate to other cortical and thalamic neurons. In the thalamus, neurons facilitate oscillatory-like fluctuations which are sent back to the different cortical areas and participate in the maintenance of the seizure. SWD are therefore initiated by a specific set of cortical neurons that propagate and generalize the epileptic discharges *via* long-distance networks giving the tempo for abnormal brain oscillations.

In conclusion, the GAERS model offers the unique opportunity to explore by different techniques the physiopathology of a common form of human epilepsy. Its high similarity with human symptoms and excellent drug predictivity facilitate the transfer of knowledge to the clinic.

Antoine Depaulis *&* ***Stéphane Charpier***

Publication

The genetic absence epilepsy rat from Strasbourg as a model to decipher the neuronal and network mechanisms of generalized idiopathic epilepsies.

Depaulis A, David O, Charpier S

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