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# Maturation of the axon initial segment in the hippocampus of the rat (CA3)

Autor: Florian Donatus Katgely
Institut / Klinik: Mannheim Center for Translational Neuroscience (MCTN). Neuroanatomy
Doktorvater: Prof. Dr. Ch. Schultz

The axon initial segment (AIS) as the site of action potential initiation is an important target for homeostatic regulation of neuronal activity. AIS plasticity manifests as shortening or lengthening of the domain or a distal or proximal shift to the soma as mechanisms to reduce or increase excitability. Effective operation of these mechanisms has been demonstrated during development for different brain areas and for states of altered neuronal input. Recent research in sensory cortices revealed that development of AIS is characterized by an initial increase of AIS length followed by a distinct and rapid shortening of AIS as a homeostatic response to a sudden increase of external input. Sensory deprivation has been shown to prevent shortening of the AIS, underlining the homeostatic nature of this mechanism. For non-sensory brain areas as e.g. the hippocampus, no sudden onset of external input is to be expected and development of AIS should follow a different pattern.

In the present thesis, it was investigated how AIS length develops in hippocampal area CA3. AIS length was assessed from birth up to adulthood in rats (P1 to P180) using multichannel immunofluorescence, confocal microscopy and morphometric analysis. AIS length steadily increased over the first 35 postnatal days with different rates and reached a maximum at day 35. Afterwards, only a very slight reduction in length up to postnatal day 180 was observed, possibly indicating fine-tuning in a mature network. There was no evidence for a period of rapid decrease of AIS length as observed in sensory cortices. Expression of the AIS scaffolding protein Ankyrin-G (AnkG) investigated via immunoblot analysis showed a complex pattern over the whole lifespan of animals and did not show a clear correlation to AIS length development.

Potential adaptive responses of the AIS to changes in network state were examined in a model of increased neuronal excitability. This investigation was conducted in collaboration with the University of Veterinary Medicine, Hannover, using a model of spontaneous recurring seizures. Hippocampal AIS in rats with induced seizures were significantly shorter as compared to healthy animals by about 12-15%. This finding is best explained as a homeostatic reaction antagonizing the underlying increased neuronal excitability. Frequency distribution of AIS lengths suggests that length reduction primarily concerns the long and especially excitable AIS. Immunoblot analysis revealed that AnkG expression was distinctly increased in animals with induced seizures compared to controls.

Overall, this study provides further evidence that the AIS is an important target for regulation of neuronal excitability not only in sensory cortices but also in the hippocampus and undergoes characteristic changes during development. Furthermore, hippocampal AIS show adaptive responses in a model of epilepsy, indicating that changes at the AIS may play a role in the pathology of epilepsy and may be important to downregulate increased neuronal excitability.