

Cerebral small vessel disease predisposes to temporal lobe epilepsy: a study in spontaneously hypertensive rats

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Experimental and clinical evidences showed that cerebral vasculature is highly sensitive to arterial hypertension. Chronic hypertension leads to morphological alterations of cerebral vessels and it is an established risk factor for clinically detected stroke, which is in turn a risk factor for epilepsy. This relation suggests that hypertension, particularly severe and uncontrolled, might increase the risk of epilepsy in the absence of prior clinically detected stroke (Zhang et al., 2010). Furthermore, it is a risk for human cerebral small vessel disease (CSVD). Renin-angiotensin system (RAS), originally known as a blood pressure controller, exists in the brain and it may be involved in the pathogenesis of neurological and psychiatric disorders including seizures (Lukawski et al., 2013). We analysed in spontaneously hypertensive rats (SHRs), a well-established animal model of hypertension and CSVD, compared to controls (Wistar-Kyoto rats, WKY) if SHRs have a propensity to certain types of epilepsy. In SHRs, it has been demonstrated that cerebral microangiopathy is initiated by early microvascular dysfunction leading to the breakdown of the blood brain barrier and an activated coagulatory state resulting in capillary and arteriolar erythrocyte accumulations (stases) (Kaiser et al., 2014). Stases are indicative of early microvascular dysfunction in SHRs. In SHRs, brain Angiotensin II receptors are mostly distributed in structures associated with cardiovascular regulation (Tchekalarova and Georgiev, 2005). SHRs could be considered as a tool for studying the link between CSVD and epilepsy. In epilepsy, clinical studies show an up-regulation of AT1 and AT2 receptors in the cortex and hippocampal formation of patients with temporal lobe epilepsy (TLE) supporting RAS involvement (Arganaraz et al., 2008). Moreover, clinical studies demonstrated that TLE predominates in patients with leukoaraiosis (Gasparini et al; 2014). Several animal models have been used to study TLE, such as those induced by kainic acid and pilocarpine, showing similarity to human phenomena (Loscher, 1997). We induced amygdala kindling, an animal model of TLE, and Pentylentetrazole (PTZ)-induced kindling, a model of generalized seizures in SHRs and suitable controls in order to establish whether hypertension and/or CSVD might give a predisposition to certain types of epilepsy. SHRs of 6 weeks of age with only hypertension in amygdala kindling model did not kindle before control group, while when they were 16 weeks of age, kindling rate in SHRs was more rapid than in WKY rats, requiring fewer afterdischarges to achieve 3 consecutive stage-5 seizures (Racine, 1972). Intraperitoneal pre-treatment (1 hour) with carbamazepine (50 mg/kg i.p.) in kindled rats (16 weeks old) of both strains had similar effects reducing seizure score from 5 to 3 while, AT1 antagonist losartan (50 mg/kg i.p.) pre-treatment (1 hour) had not effects on seizure score. In PTZ kindling model, SHRs and WKY rats of 16 weeks of age reached a stage 5 seizure intensity after about 6 weeks of treatment and, therefore, kindling was achieved with about 16 injections of PTZ. In conclusion, these results indicate that SHR rats have a higher susceptibility through the progressive development of focal and secondarily generalized seizures upon repeated electrical stimulation of a limbic brain region in comparison to Wistar Kyoto control rats, while they do not differ in the development of generalized seizures.

References

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