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Research Report

Increased susceptibility to pentetrazol-induced seizures in developing rats after cortical photothrombotic ischemic stroke at P7

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ABSTRACT

Perinatal stroke is a common cerebrovascular disorder affecting 1 in every 4000 births; typically associated with epilepsy. We sought to determine seizure susceptibility to pentylentetrazol (PTZ)-induced seizures in developing rats with a history of photothrombotic lesion of sensorimotor cortex induced at postnatal day 7. Lesioned animals were tested at P12 or P25 and compared with sham-operated controls. Three models of epileptic seizures were elicited by PTZ: episodes of spike-and-wave rhythm, minimal clonic seizures and generalized tonic–clonic seizures. PTZ (60 and 100 mg/kg) was administered subcutaneously to assess seizure occurrence, latency and severity. In addition, episodes of rhythmic EEG activity were analyzed at P25 following successive interperitoneal 20 and 40 mg/kg PTZ administration. There was only one significant change in convulsive seizures—decreased latency of generalized seizures in lesioned 12-day-old animals. EEG study demonstrated marked difference between lesioned and control rats. Lesioned rats had longer latencies and longer durations of the first rhythmic episode (following 20 mg/kg PTZ) as compared to controls. After 40 mg/kg of PTZ, 7 in 8 leisioned and 1 in 8 control rats exhibited clonic seizures. Cortical ischemic lesion during early development affected differently the susceptibility of rat's brain to three types of PTZ-induced seizures 5 and 18 days post photothrombotic insults.

1. Introduction

Epilepsy is a neurological condition characterized by spontaneous recurrent epileptic seizures. These seizures often appear as a consequence of numerous pathologies including stroke resulting in brain damage and neuronal hyperexcitability (Friedman et al., 2009; Kelly et al., 2001). Initial brain damage that leads to epilepsy is frequent in the early stages of brain development and initial seizure induction is highest in the first month of life (Hauser et al., 1993). The incidence of stroke in these perinatal periods is said to be 1 in every 4000 term births (Estan and Hope, 1997; Lynch and Nelson, 2001), this figure is likely higher, but due to the lack of visible symptoms during these early postnatal periods, perinatal stroke cases are poorly documented. Furthermore, stroke is a leading cerebrovascular disorder occurring around the time

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of birth, associated with high social and medical cost to society, due to long-term co-morbidity including epilepsy (Lynch, 2009; Sran and Baumann, 1988; Sreenan et al., 2000).

There are several models of focal as well as diffuse ischemic brain damage elaborated mostly in adult experimental animals. Among these models is photothrombosis, a technique based on thrombus-producing photochemical principle, used to mimic active clot formation leading to ischemic damage. It represents a model of focal cortical ischemia that simulates the occlusion-initiating events in human stroke (Watson and Prado, 2009). Photosensitive dyes such as Bengal Rose or Erythosin B, commonly used for this purpose are activated by laser light forming free radicals and endothelial cell damage, aggregation of platelets and eventually occlusion of the vessel. We applied this technique in immature rats at postnatal day 7, to analyze the consequences that stroke of sensorimotor cortex has on seizure susceptibility to PTZ-induced seizures, as early as 5 and 18 days after photothrombosis.

Pentylentetrazol (PTZ) exhibits the convulsant action mainly by antagonism of GABA-A receptors but other mechanisms are participating (e.g. effect on potassium channels — Louvel and Heinemann, 1981; Madeja et al., 1994), it effortlessly passes though the blood–brain barrier (BBB) and is widely used to induce behavioral seizures and allows the assessment of brain excitability (Kliouéva et al., 2001). For the analysis of changes in post stroke susceptibility to PTZ-induced seizures in immature rats, we evaluated 3 types of epileptic seizures elicited by a systemic administration of increasing doses of PTZ (Velíšek et al., 1992): nonconvulsive seizures (rhythmic EEG spike-and-wave activity) generated in the cortico-thalamo-cortical circuits (Snead, 1992), minimal clonic seizures (mS) that are generated in the basal forebrain, and generalized tonic–clonic seizures (GTCS) generated in the brainstem (Browning and Nelson, 1985). All these models are routinely used in our laboratory and their development in postnatal rats was described (Mareš, 1998; Tchekalarova et al., 2009, 2010; Velíšek et al., 1992). Rat pups were studied at two different ages—12 and 25 days according to brain development corresponding to human early postnatal stages and school going periods respectively (Dobbing, 1970; Andersen, 2003).

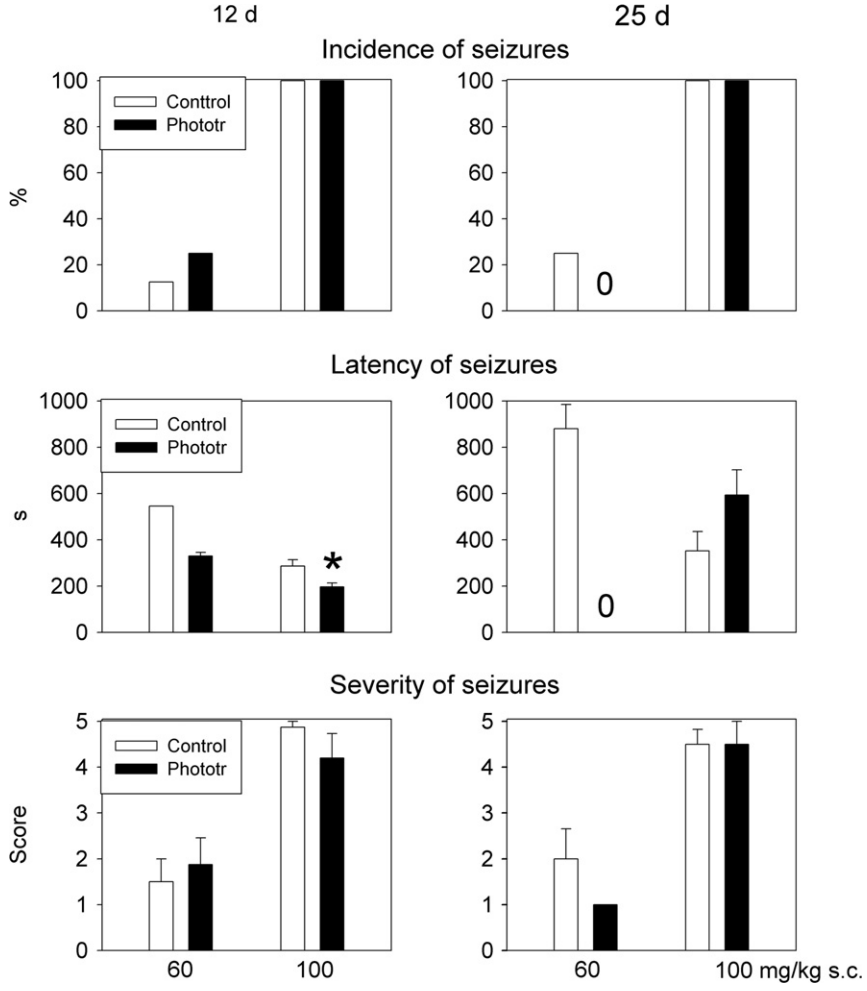

Fig. 1 – PTZ-induced seizures in 12- (left graphs) and 25-day-old rats (right graphs). From top to bottom: incidence of seizures, i.e. percentage of rats exhibiting seizures; latency of seizures (mean+S.E.M.); severity of seizures (mean+S.E.M.) evaluated by a five-point scale (Pohl and Mareš 1987). White columns — sham-operated controls with Bengal rose administration; black columns — rats with a photothrombotic lesion. Abscissas: two doses of PTZ (60 and 100 mg/kg s.c.), ordinates from top to bottom: percents of rats; latency in seconds; five-point scale.