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Review

Audiogenic kindling and secondary subcortico-cortical epileptogenesis: Behavioral correlates and electrographic features

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ABSTRACT

Human epilepsy is usually considered to result from cortical pathology, but animal studies show that the cortex may be secondarily involved in epileptogenesis, and cortical seizures may be triggered by extracortical mechanisms. In the audiogenic kindling model, recurrent subcortical (brainstem-driven) seizures induce secondary epileptic activation of the cortex. The present review focuses on behavioral and electrographic features of the subcortico-cortical epileptogenesis: (1) behavioral expressions of traditional and mild paradigms of audiogenic kindling produced by full-blown (generalized) and minimal (focal) audiogenic seizures, respectively; (2) electrographic manifestations of secondary epileptic activation of the cortex — cortical epileptic discharge and cortical spreading depression; and (3) persistent individual asymmetry of minimal audiogenic seizures and secondary cortical events produced by their repetition. The characteristics of audiogenic kindling suggest that this model represents a unique experimental approach to studying cortical epileptogenesis and network aspects of epilepsy.

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1. Introduction

Epilepsy is a network disorder associated with abnormal interactions between neurons and groups of neurons at the system level [1–3]. In both animals and humans, recurrent seizures may cause a permanent modification of neuronal networks that leads to a progressive worsening of chronic epilepsy over time, i.e., secondary epileptogenesis [4]. An excellent model for experimental analysis of the process is kindling [5,6]. Progressive intensification of repeatedly induced seizures during kindling reflects the facilitation of network activity and long-lasting increase in neuronal excitability of remote brain regions. As a result, seizures initially involving a circumscribed neuronal network progressively engage additional cortical and subcortical circuits. The kindling-induced expansion of seizure networks is manifested as a change in the phenotype of the expressed motor seizures [6]. In the classic kindling model produced by direct electrical stimulation of the amygdala, a low-intensity stimulus initially produces a weak, short, localized seizure response with minimal behavioral accompaniment. After repeated stimulation, an exposure to the same stimulus evokes a prolonged, intense seizure invading multiple cerebral structures and involving corticolimbic and subcortical networks [5,6]. Thus, the kindling model provides information about patterns of seizure generalization throughout the brain and susceptibility of brain regions to secondary epileptogenic changes.

In audiogenic kindling, epileptic activation of corticolimbic networks is a result of secondary epileptogenesis produced by repeated brainstem-driven audiogenic seizures (AS) [7–9]. Repetition of the subcortical seizures elicited by sound stimulation of susceptible rodents leads to bottom-up spread of epileptic discharges and secondary development of corticolimbic seizures. The seizure network modification manifests as a change in the phenotype of audiogenic seizures and development of epileptiform activity in the cortex.

The first description of audiogenic kindling dates back to 1960 when the development of a new forebrain-dependent component (myoclonic jerks) with repeated audiogenic seizures was reported in Krushinsky–Molodkina (KM) rats [10,11]. In 1987, a similar phenomenon was described in Wistar rats inbred for AS in Strasbourg, and the term "audiogenic kindling" was introduced [7] by analogy with the kindling process provoked by intracerebral electrical stimulation [6]. Later, audiogenic kindling was reported in genetically epilepsy-prone rats (GEPRs) [8], Wistar Audiogenic Rats (WARs) [9], and rats of WAG/Rij strain with mixed (absence and audiogenic) epilepsy [12].

Because the initiation of sound-induced seizures involves the auditory system, it has been possible to identify most brain structures within the neuronal network underlying audiogenic kindling. The primary ictogenic zone of audiogenic seizures locates in the inferior colliculus (IC), the major auditory processing center of the brainstem [13–15]. In

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rats with audiogenic epilepsy, this brainstem nucleus exhibits intrinsic epileptogenicity as a result of local deficit in GABAergic inhibition [16]. Efferent pathways for the expression of audiogenic seizures include brainstem reticular formation and reticulospinal pathways [3,15]. Upstream seizure generalization during audiogenic kindling occurs via the thalamo-amygdala pathway [16–18]. An increase in the efficacy of the acoustic–limbic pathway [17], involved in fear conditioning to auditory stimulus [19], is supposed to be an important pathophysiological mechanism of network modifications produced by repeated audiogenic seizures [3]. Finally, with the seizure repetition, corticolimbic networks become progressively sensitized that ultimately leads to the development of cortical seizures in animals with audiogenic epilepsy.

The amygdala is a critical player in the network modifications during audiogenic kindling [20,21]. Audiogenically kindled seizures can be suppressed by local inactivation of the amygdala [20,21] or can be temporarily mimicked by pharmacological activation of the structure in nonkindled rats [22,23]. During audiogenic kindling, the amygdala undergoes plastic changes similar to those occurring in electrical kindling of this structure [24]. Rats subjected to audiogenic kindling exhibit positive transfer to subsequent electrical kindling of the amygdala [20,25,26]. Therefore, despite the difference in principal pathways involved in seizure triggering, electrically and audiogenically kindled seizures seem to enhance seizure susceptibility of the same corticolimbic networks [20,27,28].

2. Behavioral patterns of audiogenic seizures acutely induced by different stimulation protocols in rats with high and low susceptibilities to audiogenic seizures

To induce audiogenic kindling, rodents are usually exposed to repeated acoustic stimulation of maximal intensity (80–120 dB) and duration (sound lasts until full seizure expression). Such intense stimulation elicits a full-blown seizure of the maximal severity attainable in a given animal. In rats with high AS susceptibility (GEPR-9s and KM rats), the sound evokes convulsions of maximal severity (score 9 according to the scale of Jobe [29]) consisting of a single episode of explosive running/myoclonic thrusts and full tonic extension of all limbs [8,30–32]. Rats with moderate AS susceptibility (GEPR-3s) exhibit seizures that start with running and terminate in generalized all-limb clonus (score 3) [8,30]. Rats with low susceptibility to AS (audiosensitive Wistar and Sprague Dawley rats) usually express a mild seizure of score 1–2, i.e., two episodes of running that may culminate in generalized clonus [30,31]. Thus, the final severity level of seizures induced by the intense sound stimulation is strain-specific and depends on innate predisposition to reflex audiogenic seizures.

In susceptible rats, sound of moderate intensity (50–60 dB) induces seizures identical to those evoked by maximal sound stimulation. Depending on the duration of acoustic stimulus, convulsive behavior of different severity could be induced in rats with high and low susceptibilities to AS (Fig. 1). In KM rats with high severity level, prolonged sound that lasts until full seizure development (the traditional stimulation paradigm) evokes full-blown AS of the maximal severity score of 9 (Fig. 1A, Table 1). The convulsions start with explosive running, then rapidly progress to severe tonic convulsions, and terminate in full all-limb tonic extension. In Wistar and WAG/Rij rats with low susceptibility to AS, the prolonged sound elicits two running bouts separated by a period of immobility (Fig. 1A, Table 1). The first bout represents a slow running that stops abruptly in a few seconds despite continued sound stimulation. After a 20- to 25-second period of immobility, the second bout of more intense and prolonged running develops, and sometimes it culminates in generalized all-limb clonic convulsions.

We developed a protocol of seizure induction by short sound stimulation interrupted with the onset of the initial running behavior [12,33]. Such stimulus only triggers a seizure while subsequent progression of the seizure occurs in the absence of epileptogenic stimulation. Therefore, a pattern of a seizure induced by this stimulus mainly depends on intrinsic mechanisms (innate epileptogenicity level and activity of seizure control networks). Our experiments have shown that such a short acoustic stimulation evokes a full-blown convulsion in KM rats and incomplete seizure response — a single episode of running — in Wistar and WAG/Rij rats (Fig. 1B). That is, in rats with high AS susceptibility, sound, regardless of its duration, evokes full-blown seizures of

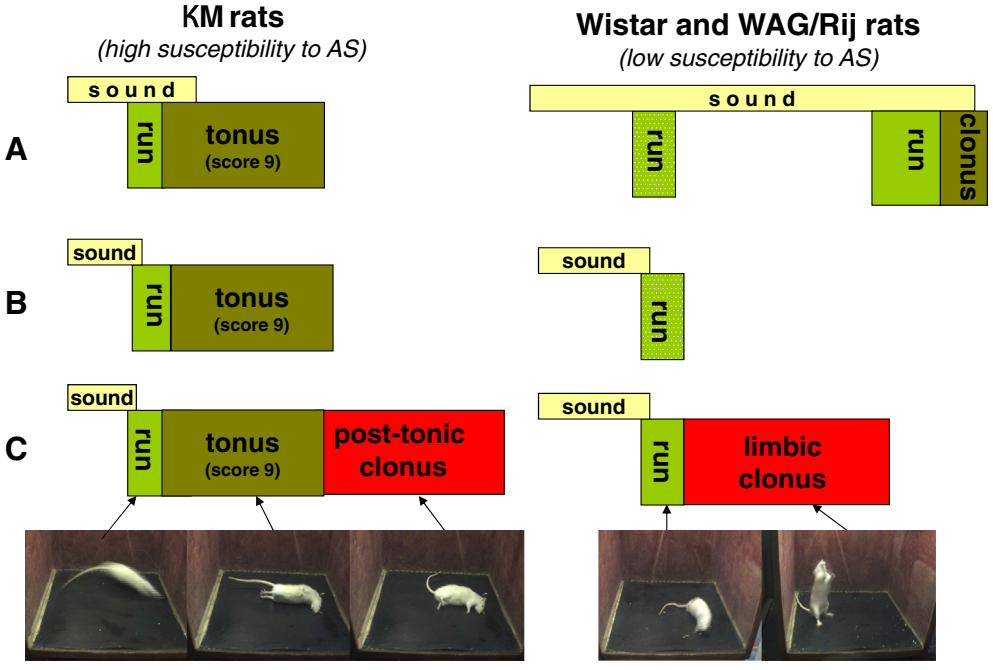

Fig. 1. Phenotypes of audiogenic seizures induced by different stimulation paradigms in rats with high (KM rats) and low (Wistar and WAG/Rij rats) susceptibilities to audiogenic seizures (AS). The figure schematically shows motor seizures induced by sound (50–60 dB) of maximal duration (i.e., lasting until a full-blown seizure develops) in nonkindled animals (A) and by the sound of minimal duration (i.e., lasting until the run onset) in nonkindled (B) and kindled (C) rats. The photographs below diagrams show behavioral patterns of respective phases of audiogenic seizures: running (run), maximal tonic convulsions (tonus), posttonic clonus, and limbic clonus.

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