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Review article

Behavioral changes in models of chemoconvulsant-induced epilepsy: A review

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ABSTRACT

Epilepsy is one of the most common neurological disorders in the general population and affects over 50 million people worldwide. Epilepsy is characterized by the presence of spontaneous recurrent seizures as a result of sudden and abnormal electrical activity in specific areas of the cerebral cortex. However, this condition encompasses much more than simply the presence of seizures. Cognitive problems and behavioral impairments are also frequent actors, as well as mood disorders. These must be precisely described in order to develop more successful pharmacological, or even behavioral, treatments. We review some of the fundamental behavioral experimental rodent protocols that have recently been applied to the study of behavioral impairments in epilepsy, particularly in epilepsy modeled by different chemoconvulsants, such as pilocarpine or kainic acid. These experimental protocols are classified into two categories: Tests designed for studying emotional factors, and those designed for studying cognitive impairments and social behavior. Behavioral impairments and adaptations identified by the use of these procedures are described.

1. Introduction

Epilepsy is the most common neurological disorder in the general population. Approximately over 50 million people worldwide suffer from epilepsy, with an estimated annual incidence ranging from 0.23 to 1.9% and a prevalence of 0.5–1%; 85% of these cases are in developing countries. Of these cases, 70% are controlled to some extent, while the overall rate of complete seizure control is 40–50% in epileptic patients (Meinardi et al., 2001; Pitkänen et al., 2016; Gschwind and Seeck, 2016).

Clinically, epilepsy is characterized by spontaneous recurrent seizures as a result of sudden and abnormal electrical activity in specific areas of the cerebral cortex. Thus, epilepsy is considered as a chronic disorder but it must be pointed out that a seizure is a symptom in and of itself. Therefore, the mere presence of seizures does not define a syndrome as epilepsy (Porter, 1986). Epilepsy has been defined by the incidence of two or more recurrent epileptic seizures over a period longer than 24 h, unprovoked by any identified cause. When seizures occur close to each other and the person does not recover between seizures, one of the most serious manifestations of epilepsy; the Status epilepticus (SE) occurs. The SE is characterized as a period of seizure activity involving two different stages that include generalized convulsive tonic-clonic seizures and continuous electrical discharges (Lévesque et al., 2016). In addition, SE is associated with a high rate of mortality and, is therefore considered a major public health problem (Sander, 1997; Fisher et al., 2014).

As previously mentioned, epilepsy and epileptic syndromes are some of the most common and heterogeneous neurological conditions. The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) has classified seizures and forms of epilepsy into two main groups according to the brain lobe where they originate as generalized and focal. Thus, this classification is based on

Abbreviations: TLE, temporal lobe epilepsy; SE, status epilepticus; DRE, drug-resistant epilsepy; KA, kainic acid; pd, post-natal days

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clinical features. Focal epilepsies are those that originate from a focus of neurons in one cerebral hemisphere and in turn are divided in two different kind: simple or complex. On the other hand, generalized epileptic seizures show bilaterally distributed networks including cortical and subcortical structures, but do not necessarily include the entire cortex. (Berg et al., 2010).

Even though about 30% of all epilepsies are idiopathic, there exist several etiological factors that contribute to the development of epilepsy, such as cerebrovascular diseases, brain tumors, and neurodegenerative disorders. In addition, epilepsy may also be due to perinatal complications, traumatic brain injuries, and infections and parasitic infestations of the central nervous system (Sander et al., 1990; Duncan et al., 2006). Moreover, in patients with epilepsy, stress and affective disorders are the most common psychiatric comorbidities (Johnson et al., 2016; Wulsin et al., 2016). Recently, various research groups have shown great interest in the role that different genes may play in susceptibility to epilepsy. Genes with possibly dissrupted or alternative functions include: CDKL5 (Cyclin-dependent kinase-like 5); STXBP1 (Syntaxin-binding protein 1), a regulator of synaptic vesicles; SCN1A (Sodium channel protein type 1 subunit alpha), a mediator of the voltage-dependent sodium ion; and ARX (Homeobox protein ARX), a transcription factor required for normal brain development (Guerrini et al., 2014; Olson et al., 2014); additionally, post-transcriptional regulation of genes may play an important role in epilepsy. Recently, the microRNA miR-101 has been shown to be critical for the regulation of excitatory and inhibitory pathways in development with targets regulating the switch in GABA signaling, and limiting early spontaneous activity, dendritic growth and excessive synapse formation (Lippi et al., 2016).

Cognitive problems and comportment impairments (e.g. memory difficulties, attention deficits, poor sleep, depression, etc.) are frequent actors in epilepsy. At present, it is generally accepted that people with epilepsy manifest some degree of cognitive impairment, with important clinical and physiological implications affecting the quality and activities of daily life (van Rijckevorsel, 2006; Seidenberg et al., 2007). In addition, up to 50% of patients have complex cognitive psychiatric, behavioral, and social problems, among which are included, hostility, impulsivity, irritability, agitation, anger, and aggressive behavior (Brodie et al., 2016). This observation emphasizes the fact that the disease of epilepsy encompasses more than simply the presence of seizures or an imbalance of the cerebral electrical activity that involved the excitatory and inhibitory balance and thus consciousness (Avoli et al., 2002).

Optimal synaptic communication is required for proper brain functions, and the slight deregulation of a synapse or changes in the balance of neurotransmitters and their receptors can lead to brain disorders. In epilepsy, the two main protagonists in the dysregulation of electrical brain conduction are γ-amino-butyric acid (GABA) and glutamate (Glu). These two molecules are, respectively, the most important inhibitory and excitatory neurotransmitters in the brain, and when the balance between them is perturbed, seizures may occur (Brooks-Kayal et al., 1998; Blumcke et al., 1999; Galovic and Koepp, 2016).

GABA is widely distributed and utilized throughout the central nervous system (CNS) and maintains an inhibitory tone that counterbalances neuronal excitation. GABA has selective effects on the different functional classes of hippocampal interneurons through two different receptors: fast-acting ionotropic GABAA receptors, and slower-acting metabotropic GABAB receptors (Bormann, 2000). Alterations in functional GABA inhibition contribute to the persistence of seizures in acquired epilepsies (Shetty and Upadhya, 2016).

Glutamate is the most prominent excitatory neurotransmitter in the human brain. Several types of ionotropic glutamate receptors have been identified and are subdivided into three groups: NMDA, AMPA, and kainate receptors. In addition to these, there are at least eight neuromodulatory metabotropic glutamate receptors (mGluRs) (Gomperts et al., 2000). With respect to this, Glu inevitably plays a role in the initiation and spread of seizure activity, and it is known that glutamate-induced excitotoxicity causes neuronal death in epilepsy (Meldrum, 1994; Cho, 2013).

Among the many different forms of epilepsy, temporal lobe epilepsy (TLE) is the most prevalent form in adults. TLE, which accounts for 60% of all cases, is related to localization and is one of the pathologies most refractory to pharmacological treatment (Téllez-Zenteno and Hernández-Ronquillo, 2012; Curia et al., 2014). The main characteristics of TLE are the presence of epileptic foci in the limbic system, particularly in the hippocampus, the entorhinal cortex, and the amygdala (Bartolomei et al., 2005). Additionally, in some cases it is possible to identify an initial insult in these areas before the symptoms related to TLE become evident. Such a situation may involve a latency period free of seizures, which occurs after limbic injury and a high incidence of unilateral mesial sclerosis in the hippocampus, producing atrophy, neuronal loss and gliosis, principally in the transition zone between CA1 and the dentate gyrus (Mathern et al., 1997; Mathern et al., 2002).

In the last 20 years, the pharmacological treatment of patients with epilepsy has evolved considerably and the use of anticonvulsants in mono- or poly- therapy has been widely and traditionally used. Unfortunately, and despite receiving treatment with different drugs used either singly or in combination, as many as 25–33% of patients present pharmacoresistance and do not benefit from the currently available antiepileptic medications; these patients with refractory epilepsy are normally referred to as drug-resistant epilepsy (DRE) (Hernández-Ronquillo et al., 2016). DRE is defined as the presence of persistent seizures despite treatment with two appropriately selected first-line antiepileptic medications that are well tolerated; DRE commonly requires surgical treatment (Oldham et al., 2015). Additionally, DRE negatively impacts quality of life and significantly increases the risk of premature death, the latter is termed “Sudden Unexpected Death in Epilepsy” (SUDEP), which represents 1% of patients evaluated for surgery (Walker and Fish, 2009).

Understanding the role of neurotransmitter deregulation in epileptogenesis might also help to identify novel biomarkers related to the prognosis, diagnosis or new therapeutic targets of epilepsy. Although our understanding of the molecular basis of epilepsy is still limited, experimental models of seizures and epilepsy have been developed and used. It is, therefore, of utmost importance to understand how pathophysiological events could be mimicked in experimental models and to compare these models with human pathological situations.

Even though animal models usually do not represent a disorder’s complete etiology, and the wide variety of pathological aspects identified in human disorders are not always present, animal models have been extensively used over the last decades in research, and have been shown to be a useful tool in the determination of different molecular and cellular processes. Models have proven to be very useful for the development of new therapeutic approaches, opening new alternatives to both the search and understanding of epilepsy and other brain disorders. When evaluating the variety of different models that exist, the most critical parameters are the understanding of the patho-physiology of epilepsy and the most common brain structures involved in the epileptogenesis. These models largely rest on the use of animals in vivo and the use of different chemoconvulsant substances, such as kainic acid (KA) and pilocarpine. These agents reproduce not only electroencephalographic features of SE, but induce a state of chronic neuronal hyperexcitability and other neuro-pathological characteristics of epilepsy, such as behavior, seizures and damage in the hippocampus, amygdala and entorhinal cortex (Ben-Ari and Cossart, 2000; Sharma et al., 2007; Buzsáki, 2015; Lévesque et al., 2016).

1.1. Epileptic model induced by pilocarpine

The systemic administration of the potent muscarinic agonist pilocarpine in rats and mice has been shown to replicate the general