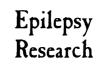


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Involvement of Scn1b and Kcna1 ion channels in audiogenic seizures and PTZ-induced epilepsy

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Abstract

We have undertaken chemical genetic approach using Qingyangshenylycosides (QYS), a natural product compound, to explore the molecular mechanisms underlying different types of epilepsy models. Two animal models were used for these studies, i.e., audiogenic seizure (AGS) and pentylenetetrazol (PTZ)-induced generalized epilepsy in DBA/2J mice. We show that the latency of AGS is prolonged and the severity of seizures (the percentages of the tonus, Tonus_%) is reduced in the QYS-treated animals. These results indicate that QYS has anticonvulsant effect on the AGS model. However, we find that administration of QYS has an opposite effects on PTZ-induced generalized epilepsy. Both the latency of the generalized epilepsy and the latency of death are decreased after QYS treatment in PTZ-induced epilepsy. We examine the molecular basis of the distinct roles of QYS in these two epilepsy models by using gene expression data. Our results show that a voltage-gated sodium channel (Scn1b) and a voltage-gated potassium channel (Kcna1) are differentially expressed in AGS and PTZ-induced epilepsy models as well as in QYS-treated animals. Our results demonstrate that a chemical genetic approach may help to reveal both the molecular mechanisms of different epilepsies and the mechanism of action of the antiepileptic drugs. © 2005 Elsevier B.V. All rights reserved.

Keywords: Qingyangshenylycosides; Audiogenic seizure; Pentylenetatrazol; Epilepsy; Anticonvulsant

1. Introduction

Abbreviations: AGS, audiogenic seizure; GABAA, gammaaminobutyric acid (GABA-A) receptor; IC, inferior colliculus; Kcna1, potassium voltage-gated channel, shaker-related subfamily, member 1; PTZ, pentylenetatrazol; QYS, Qingyangshenylycosides; Scn1b, sodium channel, voltage gated, type I, beta polypeptide

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Epilepsy is the most common neurological disorder after stroke (Loscher, 2002). Animal models for seizure and epilepsy have played fundamental role in understanding of the physiological and pathological pathways associated with human epilepsy and in testing novel antiepileptic drugs (AEDs) (Sarkisian, 2001). Many epilepsy animal models have been developed in recent years, including genetic animal models,

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chemical-induced epilepsy models and kindling models (Loscher, 1997; Sarkisian, 2001). Extensive studies using these animal models have helped to understand the pathology and etiology of epilepsy. Further studies at molecular level have demonstrated that a number of genes participating in the excitatory or inhibitory pathways of synaptic activity are involved in the disease. Some of these genes, such as GABAA receptor, sodium channels, potassium channels and carbonic anhydrase, have been proven as effective therapeutic targets for drug development (Bertrand et al., 2003; Kwan et al., 2001; Laughlin et al., 2002; Loscher et al., 1989). Indeed, a number of antiepileptic drugs such as carbamazepine, valproic acid, phenytoin, lamotrigine and phenobarbital, have been shown to exert their antiepileptic action through inhibiting neuronal hyperexcitability, modifying synaptic plasticity and regulating excessive transmitter release in the brain (Danielsson et al., 2003; Kwan et al., 2001; Sankar and Holmes, 2004; Xie and Hagan, 1998; Yogeeswari et al., 2004).

Available evidence suggests that physiological basis of audiogenic seizure (AGS) and pentylenetetrazol (PTZ)-induced epilepsy could be different (Xie and Hagan, 1998), although both models are considered to be similar to primary tonic-clonic generalized epilepsy of human (Bradford, 1995). Generation and propagation of AGS requires activation of brainstem auditory pathways, initiation is known to occur largely through the midbrain inferior colliculus (IC), but subcortical and forebrain structures may also be involved (Chakravarty and Faingold, 1999; Eells et al., 1997; Faingold, 2002; Faingold et al., 1992; Kwon and Pierson, 1997; Yang et al., 2003). However, PTZinduced epilepsy is known to be generated and propagated mainly through hippocampus (Blair et al., 1999). These studies suggested that there could be distinct mechanisms for AGS and PTZ-induced epilepsy at the molecular level. Therefore, understanding the molecular mechanisms and identification associated genes may unravel specific therapeutic targets for different forms of epilepsy.

We undertook a chemical genetic approach using the natural product compound Qingyangshenylycosides (QYS) as a tool to explore molecular mechanisms of different types of epilepsy. It has been shown that QYS has a significant anticonvulsant action on kindling effect (Kuang et al., 1981; Mu et al., 1986; Pei et al., 1987), rat audiogenic seizures (Fei et al., 1981; Mu et al., 1986; Pei et al., 1987) and electroshock seizure (Kuang et al., 1981). We have found that the anticonvulsant drug QYS could suppress audiogenic seizure in DBA/2J mice. However, here we report that the drug accelerates the generation and propagation of PTZ-induced epilepsy in the same strain of mice. The opposite effects of QYS on these two types of epilepsy suggest that different brain signalling pathways might be involved in these two disease models. To investigate the molecular mechanism of different types of epilepsy and the mechanism of action of QYS, we examined the expression of potentially important genes in AGS and PTZ-induced epilepsy models after OYS treatment. Our results reveal distinct effects of QYS on expression of ion channels in these two disease models. Further studies might help to understand molecular basis of different forms of human epilepsy.

2. Materials and methods

2.1. Drugs

QYS (supplied by Yunnan Baiyao Group Co. Ltd.) was dissolved in 1.5% Tween saline, filtered and stored at 4 °C. The main components of QYS were Otophylloside A and Otophylloside B (Fig. 1) (Mu et al., 1986). Pentylenetetrzol (Sigma) was dissolved in the saline and stored at 4 °C.

2.2. Animals

Three to four- and eight-week-old adult DBA/2J mice were used. Animals were housed with free access to food and water in a standard laboratory conditions with natural light–dark cycle at 21 ± 1 °C.

2.3. Audiogenic seizure model

Four groups of young DBA mice were used in this experiment. The mice received an intra-peritoneal injections of saline (control) or different dosage of QYS (100, 150 and 250 mg/kg) every 24 h for two continuous treatments (Kuang et al., 1981). After the treatment, animals were put into a glass-made chamber ($40 \text{ cm} \times 40 \text{ cm} \times 30 \text{ cm}$) and allowed to explore freely. The animals were then exposed to high-intensity

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