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Topiramate and zonisamide prevent paradoxical intoxication induced by carbamazepine and phenytoin

Satoshi Yamamura[a], Tatsuya Hamaguchi[a], Keiko Ohoyama[a], Yoshihiro Sugiura[b], Dai Suzuki[a], Shinich Kanehara[a], Masanori Nakagawa[a], Eishi Motomura[a], Takuya Matsumoto[a], Hisashi Tanii[a], Takashi Shiroyama[a], Motohiro Okada[a,*]

[a] *Department of Psychiatry, Division of Neuroscience, Graduate School of Medicine, Mie University, 2-174 Edobashi, Tsu, Mie 514-8507, Japan*
[b] *Department of Neurology, School of Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan*

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Summary The mechanisms of paradoxical aggravation of epileptic seizures induced by selected antiepileptic drugs (AEDs) remain unclear. The present study addressed this issue by determining the seizure-threshold doses of carbamazepine (CBZ) and phenytoin (PHT), as well the dose-dependent effects of CBZ, PHT, and carbonic anhydrase-inhibiting AEDs, acetazolamide (AZM), topiramate (TPM), and zonisamide (ZNS), on neurotransmitter release in rat hippocampus. The dose-dependent effects of AEDs on hippocampal extracellular levels of glutamate (Glu), GABA, norepinephrine (NE), dopamine (DA), and serotonin (5-HT) were determined by microdialysis with high-speed and high-sensitive extreme liquid chromatography. Proconvulsive effects of AEDs were determined by telemetric-electrocorticography. Therapeutically relevant doses of AZM, CBZ, TPM, and ZNS increased hippocampal extracellular levels of GABA, NE, DA, and 5-HT, while PHT had no effect. Supratherapeutic doses of AZM, CBZ, PHT, TPM, and ZNS decreased extracellular levels of GABA, NE, DA, and 5-HT, without affecting Glu levels. Toxic doses of CBZ and PHT produced seizures (paradoxical intoxication), markedly increasing all transmitter levels, but TPM and ZNS even at toxic doses did not produce seizure. Co-administration experiments showed that therapeutically relevant doses of CBZ or PHT reduced the seizure-threshold doses of PHT or CBZ, respectively. In contrast, therapeutically relevant doses of AZM, TPM, and ZNS elevated the seizure-threshold doses of CBZ and PHT. These results

* Corresponding author. Tel.: +81 59 231 5018; fax: +81 59 231 5208.
E-mail address: okadamot@clin.medic.mie-u.ac.jp (M. Okada).

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suggested that blockade of high percentage of the population of voltage-dependent sodium channels by CBZ and PHT might be important in inducing paradoxical intoxication/reaction, and that inhibition of carbonic anhydrase inhibits this effect. TPM and ZNS are candidate first-choice agents in treatment of epilepsy when first-line AEDs are ineffective.

Introduction

Epilepsy ranks high on the list of chronic human disorders and the major goal of pharmacological therapy for epilepsy is complete freedom from seizures. When patients do not become seizure free on their first- or second-choice antiepileptic drugs (AEDs), physicians and patients choose sequential monotherapy (increasing dosage of the same AED) or combination therapy (addition of another AED). However, epileptic seizures are often paradoxically worsened by either approach (Bourgeois, 2003; Chaves and Sander, 2005; Deckers et al., 2003; Elger et al., 1998; Osorio et al., 1989; Perucca et al., 1998; Troupin and Ojemann, 1975).''Paradoxical intoxication'' describes the effect whereby increasing serum AED concentrations to the supratherapeutic range during sequential monotherapy aggravates epileptic seizures, and reducing the serum levels back to the therapeutic range improves the worsened seizures (Bourgeois, 2003; Chaves and Sander, 2005; Deckers et al., 2003; Osorio et al., 1989; Perucca et al., 1998; Troupin and Ojemann, 1975). In contrast, ''paradoxical reaction'' occurs during the treatment of intractable epilepsy, when despite maintaining serum AED concentrations within the therapeutic range, increasing the number of administered AED often paradoxically worsens the seizure frequencies or provokes the appearance of new seizure types (Bourgeois, 2003; Chaves and Sander, 2005; Deckers et al., 2003; Perucca et al., 1998; Troupin and Ojemann, 1975). The first-line voltage-dependent sodium channel (VDSC)-inhibiting AEDs, carbamazepine (CBZ) and phenytoin (PHT), are implicated most frequently in reports of paradoxical intoxication and paradoxical reaction. However, the mechanisms underpinning these phenomena remain to be clarified (Bourgeois, 2003; Chaves and Sander, 2005; Deckers et al., 2003; Elger et al., 1998).

Unlike CBZ and PHT, the second-generation AEDs, topiramate (TPM) and zonisamide (ZNS), are relatively safe and generally do not induce paradoxical intoxication/reaction (Chaves and Sander, 2005). These two AEDs are broad-spectrum antiepileptics that act through multiple pharmacological mechanisms. ZNS inhibits VDSC, T-type voltage-sensitive calcium channel (VSCC), intraneuronal calcium-induced calcium releasing (CICR), and glutamate (Glu) release induced by hyperneuronal excitation and carbonic anhydrase (Kito et al., 1996; Okada et al., 1992, 1995, 1999, 2005; Shank et al., 2008; Suzuki et al., 1992; Yoshida et al., 2005). TPM inhibits VDSC, L-type VSCC, CICR, kainate-induced currents, and carbonic anhydrase (Angehagen et al., 2004; Herrero et al., 2002; Okada et al., 2005; Shank et al., 2008; Zhang et al., 2000).

Although several reports have discussed the occurrence of paradoxical intoxication/reaction in a broad context with special reference to drugs with proconvulsant activity, the specific role of paradoxical intoxication/reaction has received relatively little attention (Bourgeois, 2003; Chaves and Sander, 2005; Elger et al., 1998; Perucca et al., 1998). Furthermore, the concept of using combination therapy to avoid the paradoxical reaction also remains to be clarified. We suggested previously that severe dysfunction of monoaminergic transmission plays an important role in PHT-induced paradoxical intoxication, since toxic doses of PHT resulted in substantial reduction in monoamine release in the striatum and hippocampus before the onset of seizures (Okada et al., 1997b). Furthermore, the pharmacological profiles of the first-line VDSC-inhibiting AEDs (CBZ and PHT) and second-generation AEDs (TPM and ZNS) suggest that inhibition of carbonic anhydrase prevents the paradoxical intoxication/reaction. Therefore, to clarify the mechanisms of paradoxical intoxication/reaction and explore the avoidance of paradoxical reaction induced by the combination therapy, we conducted the following studies. (1) Determination of seizure-threshold doses of CBZ, PHT, ZNS and TPM. (2) Determination of the dose-dependent effects of hippocampal releases of norepinephrine (NE), dopamine (DA), serotonin (5-HT), GABA and Glu. (3) Determination of the effects of therapeutically relevant doses of TPM and ZNS on paradoxical intoxication/reaction and neurotransmitter release.

Materials and methods

Experimental animals

All experimental protocols accorded with the specifications of the Ethical Committee of Mie University, and met the guidelines of the responsible governmental agency. Male Sprague—Dawley rats (SLC, Shizuoka, Japan), weighing 250—300 g, were housed under conditions of constant temperature at 22 ± 2 °C with a 12 h light—dark cycle.

Chemicals

The following drugs were used in this study: carbamazepine (CBZ: Wako Chemicals, Osaka, Japan), phenytoin sodium (PHT: Wako Chemicals), topiramate (TPM: Sigma—Aldrich, St. Louis, MO), zonisamide (ZNS: Dainippon-Sumitomo Pharma, Osaka, Japan), acetazolamide (AZM: Sigma), and VDSC inhibitor, tetrodotoxin (TTX: Wako Chemicals). AZM, CBZ, PHT, TPM, and ZNS were dissolved in saline containing 1% (vol/vol) dimethyl sulfoxide. The PHT solution was adjusted to pH 7.0 using phosphate.

Microdialysis system preparation

Each rat was placed in a stereotaxic frame and kept under anesthesia using 1.8% isoflurane. A concentric I-type dialysis probe (A-I-5-03, 0.22 mm diameter; 3 mm exposed membrane; Eicom,