Available online at www.sciencedirect.com
SCIENCE DIRECT
Neuropharmacology 50 (2006) 1059–1071
NEURO PHARMACOLOGY
www.elsevier.com/locate/neuropharm

Effects of some neurosteroids injected into some brain areas of WAG/Rij rats, an animal model of generalized absence epilepsy

Rita Citraro [a], Emilio Russo [a], Eugenio Donato Di Paola [a], Guido Ferreri Ibbadu [a], Santo Gratteri [b], Rosario Marra [b], Giovambattista De Sarro [a,*]

[a] *Section of Pharmacology, Department of Experimental and Clinical Medicine, Faculty of Medicine and Surgery, University of Catanzaro, Policlinico Mater Domini, Via T. Campanella, 115, 88100 Catanzaro, Italy*
[b] *ISBAF CNR, Department of Pharmacology, Faculty of Pharmacy, University of Catanzaro, Catanzaro, Italy*

Received 9 November 2005; received in revised form 30 January 2006; accepted 20 February 2006

Abstract

Neurosteroids are synthesized in the brain and have been demonstrated to modulate various cerebral functions. Allopregnanolone (3α-hydroxy-5α-pregnan-20-one), a naturally occurring neurosteroid, and ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one), a synthetic derivative, are two neurosteroids acting as positive allosteric modulators of the $GABA_A$ receptor complex acting on a specific steroid recognition site. Both agents antagonize generalized tonic-clonic seizures in various animal models of epilepsy. Pregnenolone sulphate (3β-hydroxy-5α-pregnen-20-one 3-sulphate; PS) is a negative allosteric modulator of $GABA_A$ receptors and a positive modulator of the NMDA receptors. We have evaluated the effects of such compounds in a genetic animal model of absence epilepsy, the WAG/Rij rat. Animals were chronically implanted with five frontoparietal cortical electrodes for electrocorticogram (EEG) recordings and bilateral guide cannulae into specific brain areas of the cortico-thalamic circuit in order to evaluate the effects of these compounds on the number and duration of epileptic spike-wave discharges (SWDs). The focal and bilateral microinjection of the two $GABA_A$ positive modulators into some thalamic nuclei (nucleus ventralis posteromedialis, nucleus reticularis thalami, nucleus ventralis posterolateralis was usually able to significantly worsen the occurrence of SWDs in WAG/Rij rats. Whereas both compounds were able to reduce the number and duration of SWDs when microinjected into the peri-oral region of the primary somatosensory cortex. The effects of PS were more complex depending on both the dose and the site of administration, generally, at low doses in thalamic nuclei and cortex, PS induced an increase of absence activity and a reduction at higher doses. These findings suggest that neurosteroids might play a role in absence epilepsies and that it might depend on the involvement of specific neuronal areas.
© 2006 Elsevier Ltd. All rights reserved.

Keywords: Absence seizures; Allopregnanolone; Ganaxolone; Pregnenolone sulphate; Neurosteroids; WAG/Rij rat; Thalamus; Primary somatosensory cortex

1. Introduction

The term *neurosteroids* refers to steroids synthesized in the nervous system; it is now clear that these endogenous substances are able to modulate the excitability of the central nervous system (CNS) through a wide variety of functions differentiated from the action on the classic steroid hormone nuclear receptors (Mensah-Nyagan et al., 1999). It has been demonstrated that several endogenous neurosteroids are able to modulate $GABA_A$ receptors (Majewska, 1992; Morrow et al., 1987, 1990; Lambert et al., 1995, 2003; Rupprecht and Holsboer, 1999; Gee et al., 1995) at low concentrations and at higher concentration they can also modulate other ligand and/or voltage gated ion channels such as NMDA and non-NMDA receptors (Majewska et al., 1986; Majewska, 1992; Wu et al., 1991; Irwin et al., 1994; Baulieu and Robel, 1990), nicotinic (Bullock et al., 1997), muscarinic (Horishita et al., 2005), glycine (Maksay et al., 2001) and σ receptors (Monnet et al., 1995; Bergeron et al., 1996).

Regarding $GABA_A$ receptors, it has been demonstrated that neurosteroids bind to a putative specific steroid recognition

* Corresponding author. Tel.: +39 0961 712323; fax: +39 0961 774424.
E-mail address: desarro@unicz.it (G. De Sarro).

0028-3908/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2006.02.011

site different from those of benzodiazepines and barbiturates (Belelli et al., 1990; Gee, 1988a; Ueno et al., 2004). This binding leads to either inhibition or potentiation of the inhibitory effects of GABA. Inhibition of GABA-receptor function produces effects ranging from anxiety and excitability to seizure susceptibility, while potentiation of GABA-ergic effects produces anticonvulsant and anxiolytic effects, sedation and hypnosis (Smith, 2002). Modulatory effects of neurosteroids at the $GABA_A$ receptor chloride channel complex have been characterized in a large number of studies: different progesterone metabolites as pregnanolone (3α-hydroxy-5β-pregnan-20-one), allopregnanolone (3α-hydroxy-5α-pregnan-20-one) and some synthetic steroids such as ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one), produce a potent enhancement of $GABA_A$ receptor responses (Harrison et al., 1987; Kokate et al., 1994, 1999; Majewska et al., 1986; Lambert et al., 1995; Peters et al., 1988) and similarly to other positive GABA modulators (benzodiazepine and barbiturates) show potent anticonvulsant, anxiolytic, sedative and hypnotic activities when administered in vivo (Belelli et al., 1989; Bitran et al., 1991; Concas et al., 1996; Kokate et al., 1994, 1999), furthermore, it has been described that neurosteroids possess a GABA-enhancing effect at low concentrations (nanomolar; positive allosteric modulation), but at higher concentrations these steroids are also able to directly open the $GABA_A$ receptor-chloride channel (Harrison et al., 1987; Lambert et al., 1995; Carter et al., 1997).

Given that the GABA-ergic neurotransmitter system is a major molecular target for antiepileptic drugs (Löscher and Nolting, 1991; Löscher and Schmidt, 1994; Bradford, 1995), focus on neurosteroids as potential therapeutic agents for the treatment of epilepsy has increased (Hawkinson et al., 1994a; Gasior et al., 1999; Czuczwar and Patsalos, 2001; Reddy, 2003). Additional interest comes from the suggested involvement of neurosteroids in the homeostatic regulation of neuronal excitability and in the pathophysiology of human epilepsy (e.g. catamenial epilepsy) (Herzog et al., 1997; Herzog, 1999; Reddy and Kulkarni, 2000; Reddy et al., 2001; Reddy and Rogawski, 2001), with allopregnanolone implicated in the regulation of seizure susceptibility in various clinical conditions, most notably catamenial epilepsy (Rogawski, 2003).

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) belongs to a novel class of neuroactive steroids called epalons, which specifically modulate the $GABA_A$ receptor in the CNS. Ganaxolone is a 3β-methylated synthetic compound that is structurally related to the endogenous neurosteroid allopregnanolone (Gasior et al., 1999; Monaghan et al., 1999). Ganaxolone is more stable than allopregnanolone, as a result of its 3β-methyl group, which prevents its metabolism and oxidation at the 3α-hydroxy moiety (Carter et al., 1997). Thus, ganaxolone might be expected to retain the anticonvulsant activity of the endogenous neurosteroid allopregnanolone while acquiring a pharmacokinetic profile that would be expected to enhance its use as an antiepileptic drug. Like allopregnanolone, ganaxolone is an efficacious anticonvulsant agent in a variety of animal seizure models, as well as in electrical and chemical kindling models (Gasior et al., 1997, 1999, 2000; Belelli et al., 1990; Kokate et al., 1994).

It has been demonstrated that ganaxolone is able to inhibit binding of the $GABA_A$ receptor ligand *t*-[^{35}S]butylbicyclophosphorothionate and enhanced binding of both the benzodiazepine site ligand [^{3}H]flunitrazepam and the GABA site ligand [^{3}H]muscimol, consistent with activity as a positive allosteric modulator of the $GABA_A$ receptor (Goodnough and Hawkinson, 1995). The profile of anticonvulsant activity obtained for ganaxolone supports clinical evaluation of this drug as an antiepileptic therapy with potential utility in the treatment of generalized absence seizures as well as simple and complex partial seizures (Carter et al., 1997). Different experiments were conducted to describe the in vitro modulatory properties of ganaxolone at the $GABA_A$ receptor complex as well as to define its in vivo preclinical anticonvulsant profile.

It has been demonstrated that ganaxolone exacerbates discharges in both the PTZ and γ-hydroxybutyric acid (GHB) model of absence seizures in rats (Snead, 1998), and also allopregnanolone and pregnenolone sulphate (PS) given systematically were able to aggravate, dose-dependently, the epileptic spike-wave activity in WAG/Rij rat, a genetic model for generalized absence epilepsy (Budziszewska et al., 1999), even if they possess opposite effects on $GABA_A$ receptor this has been justified by the action of PS on NMDA receptors.

Because genetic models of absence seizures may share mechanisms that underlie absence seizures in humans (Löscher and Schmidt, 1988; Noebels, 1984, 1986), these models have great potential to be predictive in affecting epileptic phenomena. Rats of the WAG/Rij inbred strain with spontaneous bilaterally synchronous generalized SWDs are widely recognized as a good genetic model of human absence epilepsy (Coenen et al., 1992; Coenen and Van Luijtelaar, 2003). Absence epilepsy, a non-convulsive epilepsy of multifactorial origin, is characterised by a sudden interruption of both physical and mental activity, without major loss of postural tone, coupled to bilateral synchronous SWDs on the EEG (Panayiotopoulos, 1997; Snead, 1995). Electrophysiological studies indicated that abnormal discharges on the EEG are generalized and cortico-thalamic network is primarily involved (Landisman et al., 2002; Blumenfeld and McCormick, 2000; Snead, 1995; Coenen and Van Luijtelaar, 2003; Bal et al., 2000; Huntsman et al., 1999). Several neurotransmitters that regulate thalamocortical functions, also including glutamate and GABA, play significant role in the pathophysiology of this type of epilepsy (Snead, 1995; Staak and Pape, 2001; Steriade, 2001; Spreafico et al., 1993; Crunelli and Leresche, 1991; Knight and Bowery, 1992).

The purpose of the present study was to ascertain the activity of some neurosteroids against absence seizures in the WAG/Rij rat model and evaluate their activity in brain areas primary involved in the generation of absence seizures (Snead, 1995; Wang and Snead, 2001; Coenen and Van Luijtelaar, 2003). Thalamic sites have been chosen according to previous reports demonstrating that nuclei of the ventrobasal complex, such as nucleus ventralis posteromedialis thalami (VPM) and nucleus ventralis posterolateralis thalami (VPL) and the

Download English Version:

https://daneshyari.com/en/article/2495212

Download Persian Version:

https://daneshyari.com/article/2495212

Daneshyari.com