Enhanced Anticonvulsant Activity of Ganaxolone after Neurosteroid Withdrawal in a Rat Model of Catamenial Epilepsy

DOODIPALA S. REDDY and MICHAEL A. ROGAWSKI

Neuronal Excitability Section, Epilepsy Research Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

Accepted for publication May 8, 2000 This paper is available online at http://www.jpet.org

ABSTRACT

Perimenstrual catamenial epilepsy, the exacerbation of seizures in association with menstruation, may in part be due to withdrawal of the progesterone metabolite allopregnanolone, a potent positive allosteric modulator of γ-aminobutyric acid (GABA) receptors. Neurosteroid replacement is a potential approach to therapy, but natural neurosteroids have poor bioavailability and may be converted to metabolites with undesired progestational activity. The synthetic neuroactive steroid ganaxolone (3α-hydroxy-3β-methyl-5α-pregnane-20-one) is an orally active analog of allopregnanolone that is not converted to the hormonally active 3-keto form. To assess the potential of ganaxolone in the treatment of catamenial seizure exacerbations, a state of persistently high serum progesterone (pseudopregnancy) was induced in 26-day-old female rats with gonadotropins, and neurosteroids were withdrawn on postnatal day 39 with finasteride, a 5α-reductase inhibitor that blocks the conversion of progesterone to allopregnanolone. Finasteride treatment during pseudopregnancy results in a reduction in the threshold for pentylenetetrazol seizures. During this state of enhanced seizure susceptibility, there was a 3-fold increase in the anticonvulsant potency of ganaxolone (control ED50 = 3.5 mg/kg; withdrawn = 1.2 mg/kg) without a change in the potency for induction of motor toxicity in the rotarod test. The plasma concentrations of ganaxolone did not differ significantly in control and withdrawn animals; the estimated plasma concentrations of ganaxolone producing 50% seizure protection were ~500 and ~225 ng/ml in control and withdrawn rats, respectively. Unlike allopregnanolone, neurosteroid withdrawal was associated with a decrease in the anticonvulsant potency of diazepam (control ED50 = 1.9 mg/kg; withdrawn = 4.1 mg/kg) and valproate (control ED50 = 279 mg/kg; withdrawn = 460 mg/kg). The enhanced anticonvulsant potency of ganaxolone after neurosteroid withdrawal supports the use of ganaxolone as a specific treatment for perimenstrual catamenial epilepsy.

Catamenial epilepsy, the recurrent exacerbation of seizures at specific times during the menstrual cycle, affects from 10 to 72% of women with epilepsy (Ansell and Clarke, 1956; Laidlaw, 1956; Rosciszewska, 1986; Tauboll et al., 1991; Duncan et al., 1993). In many women with catamenial epilepsy, catamenial seizure clustering occurs just before or during menstruation, in association with a fall in serum progesterone levels (Newmark and Penry, 1980; Herzog et al., 1997). Progesterone has anticonvulsant properties in large part due to its conversion to the neuroactive steroid allopregnanolone, a potent positive modulator of γ-aminobutyric acid (GABA) receptors (Laidlaw, 1956; Kokate et al., 1994, 1999). Thus, perimenstrual seizure exacerbations in women with catamenial epilepsy could be related to neurosteroid withdrawal. Although natural progesterone therapy benefits some women with catamenial epilepsy (Herzog, 1986, 1995), it may be associated with undesired hormonal side effects. GABA receptor-modulating neurosteroids, which are devoid of such hormonal actions, may provide a rational alternative approach to therapy (Reddy and Kulkarni, 2000). However, certain obstacles prevent the clinical use of endogenously occurring neurosteroids. Importantly, natural neurosteroids such as allopregnanolone have low bioavailability because they are rapidly inactivated and eliminated by glucuronide or sulfate conjugation at the 3α-hydroxyl group. In addition, the 3α-hydroxyl group of allopregnanolone may undergo oxidation to the ketone, restoring activity at steroid hormone receptors (Rupprecht et al., 1993). Ganaxolone (CCD 1042; 3α-hydroxy-3β-methyl-5α-pregnane-20-one), the synthetic 3β-methyl analog of allopregnanolone, overcomes these limitations (Carter et al., 1997). Like allopregnanolone, ganaxolone is a positive allosteric modulator of GABA receptors and is an effective anticonvulsant in the pentylenetetrazol (PTZ) seizure test as

ABBREVIATIONS: GABA, γ-aminobutyric acid; PTZ, pentylenetetrazol; CL, confidence limits.
well as in other anticonvulsant screening models (Carter et al., 1997; Gasior et al., 1997). However, ganaxolone is orally active, and adequate blood levels can be maintained in human subjects with two or three times daily dosing (Monaehan et al., 1997). In addition, although ganaxolone is extensively metabolized, the potentially hormonally active 3-keto derivative is not formed.

To evaluate the potential of ganaxolone in the treatment of perimenstrual seizure exacerbations, we developed a rat model of catamenial epilepsy in which female pseudopregnant rats were abruptly withdrawn from neurosteroids to simulate the drop occurring in women before the menses. Pseudopregnancy, a state in which progesterone and allopregnanolone are chronically elevated, was produced by gonadotropin treatment. Neurosteroid withdrawal was induced by the administration of finasteride, a 5α-reductase inhibitor that blocks the conversion of progesterone to allopregnanolone (Azollina et al., 1997). After neurosteroid withdrawal, animals exhibit a marked enhancement in seizure susceptibility when challenged with PTZ. Unexpectedly, we found that the anticonvulsant potency of ganaxolone was enhanced in the period after neurosteroid withdrawal, whereas the potencies of two reference anticonvulsants diazepam and valproate were reduced.

### Materials and Methods

**Animals.** Female 26-day-old (70–80 g) and 40- to 45-day-old (200–250 g) Sprague-Dawley rats (Taconic) were housed in groups of four under a 12-h light/dark cycle in an environmentally controlled animal facility. Animals were allowed to acclimatize with free access to food and water for a 24-h period before use. All procedures were performed in strict compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals under a protocol approved by the National Institutes of Health Animal Use Committee.

**Pseudopregnancy Model of Catamenial Epilepsy.** Rats were injected with pregnant mare serum gonadotropin (20 IU/rat s.c.) at 10:00 AM on postnatal day 27 followed 48 h later by human chorionic gonadotropin (10 IU/rat s.c.). The day of human chorionic gonadotropin treatment (day 29) was considered day 0 of pseudopregnancy. At 11:00 AM on day 11 of pseudopregnancy, neurosteroid withdrawal was induced with finasteride (100 mg/kg in 50% ethanol mixed with 0.2 ml of blank rat plasma). At 24 h after finasteride treatment, plasma allopregnanolone levels were reduced from 44.5 to 6.4 ng/ml; there was no effect on serum progesterone concentrations as high as 50% failed to affect PTZ seizures. Diazepam and sodium valproate were dissolved in sterile isotonic saline. The diazepam solution contained a maximum of 20% propylene glycol and 5% ethyl alcohol. Drug solutions were administered s.c. or i.p. in a volume equaling 1% of the animal's body weight. Ganaxolone was a gift of CoCensys (Irvine, CA). Epiallopregnanolone (3β-hydroxy-5α-pregnan-20-one) was obtained from Steraloids (Newport, RI). Diazepam injection was obtained from Elkins-Sinn (Cherry Hill, NJ). All other drugs and hormones were obtained from Sigma Chemical Co. (St. Louis, MO).

**Data Analysis.** To construct dose-effect curves, drugs were tested at several doses spanning the dose producing seizures in 50% of animals (CD50), or resulting in 50% seizure protection (ED50) or motor toxicity (TD50). Each group consisted of six to eight rats. CD50, ED50, and TD50 values with 95% confidence limits (CL) were determined by log-probit analysis using the Litchfield and Wilcoxon procedure (PHARMA/PCS Version 4.2; Microcomputer Specialists, Philadelphia, PA). Dose-response data were fit to the logistic function 100/[1 + (D /Dx)]n where x is the dose administered; Dx is either the CD50, ED50 or TD50 and n is an empirical parameter describing the steepness of fit. When appropriate, the n values were determined simultaneously using ALLFIT 2.7 (abs.cit.nih.gov/locate/allfit/; De Lean et al., 1978). The significance of differences between the dose-response curves was determined using the Litchfield-Wilcoxon x2 test, where the criterion for statistical significance was P < .05. Protective index, a quantitative measure of the margin between doses producing anticonvulsant protection and motor toxicity, was calculated by dividing the TD50 value by the ED50 value. Statistical differences among mean plasma ganaxolone levels were analyzed by one-way ANOVA followed by Student's t test.

### Results

**Lack of Effect of Finasteride on Seizure Susceptibility.** To confirm that finasteride treatment as in the pseudo-
pregnancy model of catamenial epilepsy does not itself alter the convulsant activity of PTZ, dose-response relationships for PTZ (30–80 mg/kg s.c.) induction of clonic seizures were determined in naive control rats 24 h after i.p. injection of vehicle or 100 mg/kg finasteride. The PTZ CD\textsubscript{50} values in the vehicle and finasteride-pretreated groups were 55 mg/kg (95% CL, 45–67; n = 45) and 57 mg/kg (95% CL, 46–69; n = 36), indicating that finasteride does not affect seizure susceptibility.

**Anticonvulsant Activity of Ganaxolone after Neurosteroid Withdrawal.** In naive female control rats, ganaxolone (0.625–15 mg/kg s.c.) protected against PTZ-induced seizures in a dose-dependent fashion (Fig. 1). Ganaxolone also protected against PTZ-induced seizures in pseudopregnant control rats and in rats that had been withdrawn from neurosteroid by finasteride treatment. In neurosteroid-withdrawn rats, the dose-response curve for anticonvulsant activity of ganaxolone was significantly (P < .05) shifted in a parallel fashion to the left from that of control rats. A marginal enhancement in the potency of ganaxolone was observed in pseudopregnant animals at dose above 1.25 mg/kg. The ED\textsubscript{50} values derived from these data are given in Table 1. There was a significant decrease (64%) in the ED\textsubscript{50} value of ganaxolone for seizure protection in neurosteroid-withdrawn rats compared with naive control animals, indicating an enhancement in the anticonvulsant potency of ganaxolone after neurosteroid withdrawal. To confirm that the enhanced potency of ganaxolone is not due to an action of finasteride unrelated to neurosteroid withdrawal, the anticonvulsant ED\textsubscript{50} value for ganaxolone was determined in naive control animals that had been pretreated 24 h earlier with 100 mg/kg finasteride. The ED\textsubscript{50} value of ganaxolone in these animals was 3.2 mg/kg (95% CL, 2.2–4.5; n = 32), which is not significantly different from the value obtained in naive control rats that had not been pretreated with finasteride (Table 1).

**Motor Toxicity of Ganaxolone.** The motor toxicity of ganaxolone (1.25–20 mg/kg s.c.) was assessed with the rotarod test. In control animals, ganaxolone induced motor impairment at doses within the same range as those that were protective in the PTZ seizure test (Fig. 2). Ganaxolone was slightly less potent in pseudopregnant control and neurosteroid-withdrawn animals, but the TD\textsubscript{50} values derived from the dose-response data (Table 1) were not significantly different. Because the anticonvulsant ED\textsubscript{50} value for ganax-

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Agent</th>
<th>PTZ Test (ED\textsubscript{50})</th>
<th>Motor Impairment (TD\textsubscript{50})</th>
<th>Protective Index (TD\textsubscript{50}/ED\textsubscript{50})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganaxolone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.46 (2.06–5.82)</td>
<td>5.61 (3.52–8.94)</td>
<td>1.62</td>
</tr>
<tr>
<td>Pseudopregnant</td>
<td>2.38 (1.33–4.26)</td>
<td>7.42 (5.23–10.53)</td>
<td>3.12</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>1.24 (0.65–2.36)</td>
<td>7.89 (5.67–10.97)</td>
<td>6.36</td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.85 (1.45–2.41)</td>
<td>1.74 (1.24–2.41)</td>
<td>0.94</td>
</tr>
<tr>
<td>Pseudopregnant</td>
<td>2.46 (1.67–3.63)</td>
<td>1.68 (1.19–2.37)</td>
<td>0.68</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>4.10 (3.11–5.42)</td>
<td>1.56 (0.98–2.49)</td>
<td>0.38</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>279 (199–391)</td>
<td>382 (282–517)</td>
<td>1.37</td>
</tr>
<tr>
<td>Pseudopregnant</td>
<td>297 (217–405)</td>
<td>325 (201–527)</td>
<td>1.09</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>460 (421–503)</td>
<td>404 (333–490)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

\( ^{a}P < .05 \) versus control (\( \chi^{2} \) test).

\( ^{b}P < .05 \) versus pseudopregnant (\( \chi^{2} \) test).

---

![Fig. 1. Protection against pentylenetetrazol-induced seizures by ganaxolone in naive control female rats, finasteride-treated (neurosteroid-withdrawn) pseudopregnant rats, and pseudopregnant control rats. Animals were injected with pentylenetetrazol 15 min after the indicated dose of ganaxolone. Each point represents data from six to eight animals. The curves indicate logistic fits to the data points; ED\textsubscript{50} values are given in Table 1.](image1)

![Fig. 2. Effects of ganaxolone in the accelerating rotarod test in control female rats, finasteride-treated (neurosteroid-withdrawn) pseudopregnant rats, and pseudopregnant control female rats. Animals were tested 15 min after ganaxolone administration. Each point represents data from six to eight animals.](image2)
alone in the PTZ test was reduced in the neurosteroid-withdrawal group, the protective index (TD₅₀/ED₅₀) was higher in neurosteroid-withdrawn than in control rats (Table 1).

**Ganaxolone Plasma Concentrations.** Ganaxolone plasma concentrations were determined 15 min after the administration of various doses of ganaxolone (0.625–7.5 mg/kg s.c.) in control and pseudopregnant neurosteroid-withdrawn rats. Plasma ganaxolone concentrations in both control and neurosteroid-withdrawn animals increased monotonically in a dose-dependent fashion (Fig. 3). Ganaxolone levels in withdrawn animals were slightly lower than those in controls with 5 and 7.5 mg/kg ganaxolone, but there were no significant differences among the data at any of the doses (P > .05). These results indicate that the enhanced anticonvulsant potency of ganaxolone in neurosteroid-withdrawn rats is not due to pharmacokinetic factors leading to increased plasma ganaxolone levels.

**Anticonvulsant Activity and Motor Toxicity of Diazepam and Valproate.** For comparison, the anticonvulsant activity and motor toxicity of diazepam and valproate were examined in control, pseudopregnant, and pseudopregnant neurosteroid-withdrawn rats. In control and pseudopregnant animals, diazepam (0.4–7.5 mg/kg i.p.) was highly effective in protecting against PTZ-induced seizures (Fig. 4 and Table 1). However, in contrast to the situation with ganaxolone, where neurosteroid withdrawal was associated with enhanced anticonvulsant activity, the anticonvulsant potency of diazepam was markedly reduced in pseudopregnant animals that had undergone neurosteroid withdrawal. As shown in Fig. 5, the motor toxicity of diazepam was similar in all three groups. Thus, the protective index for diazepam was reduced in animals that experienced neurosteroid withdrawal (Table 1).

Valproate (100–800 mg/kg i.p.) was also effective in protecting against PTZ-induced seizures in control and pseudopregnant animals (Fig. 6 and Table 1). As with diazepam, there was a reduction in the potency of valproate after neurosteroid withdrawal, and there appeared to be a steepening of the dose-response curve. Moreover, like diazepam, neurosteroid withdrawal was not associated with a significant change in the motor toxicity of valproate (Fig. 7), so the protective index of valproate was also reduced in withdrawn animals (Table 1).

**Discussion**

The principal observation in this study is that the anticonvulsant potency of ganaxolone is enhanced in a model of...
perimenstrual (progesterone withdrawal type) catamenial epilepsy. There was no corresponding increase in the motor toxicity of ganaxolone. This suggests that the potentiated anticonvulsant activity of ganaxolone results from specific alterations in the brain mechanisms responsible for seizures and is not due to pharmacokinetic factors. Although the protective index of ganaxolone compares unfavorably with that of many conventional anticonvulsant agents, diazepam and valproate, were substantially reduced after neurosteroid withdrawal. Thus, neurosteroid-derived anticonvulsants such as ganaxolone may be particularly suited for the treatment of catamenial seizure exacerbations, which are often resistant to therapy with conventional anticonvulsants (Newmark and Penry, 1980).

The measurements of plasma ganaxolone levels allow us to estimate the plasma concentrations associated with seizure protection and motor toxicity. In control and neurosteroid-withdrawn animals, the threshold plasma concentrations for seizure protection were 200 to 250 and 100 ng/ml, respectively, and the estimated plasma concentrations producing 50% seizure protection were in the range of 450 to 550 and 200 to 250 ng/ml. Thus, ganaxolone protects against the PTZ-induced seizures in neurosteroid-withdrawn rats at plasma concentrations that are not anticonvulsant in control animals.

The animal model of catamenial epilepsy used in this study was designed to simulate the most common form of catamenial epilepsy in which the frequency of seizures increases in the perimenstrual period. Pseudopregnancy was induced by treatment with gonadotropins, resulting in increased ovarian production of progesterone and its 5α- and 3α-A-ring-reduced metabolite allopregnanolone. Diestrous plasma allopregnanolone levels in the rat are 9.3 ng/ml, and on day 12 of pseudopregnancy, the plasma levels of allopregnanolone are elevated 5-fold to 44.5 ng/ml (D. S. Reddy, H.-Y. Kim, and M. A. Rogawski, unpublished observations). The administration of the 5α-reductase inhibitor finasteride causes a fall in plasma allopregnanolone to a level of 6.4 ng/ml (24 h after dosing), which is modestly below that in the diestrous period. This fall in allopregnanolone is associated with a marked enhancement in the susceptibility to PTZ seizures (Frye and Bayon, 1998; Moran and Smith, 1998). It is attractive to speculate that a similar increase in seizure susceptibility accounts for the exacerbation of seizures in women with perimenstrual catamenial epilepsy. Although the cause of the enhanced seizure susceptibility is not well understood, there is some evidence that allopregnanolone withdrawal is associated with changes in the kinetic properties of GABAA receptors that predispose to heightened brain excitability (Smith et al., 1998). While finasteride may reduce serum allopregnanolone below control diestrous levels, Smith et al. (1998) have reported that brain levels do not fall below control levels at 24 h. Thus, the enhanced seizure susceptibility after finasteride treatment is not due to an absolute neurosteroid deficiency, and this supports the view that the heightened susceptibility is due to changes in GABAA receptor properties. In nonpseudopregnant animals, finasteride pre-treatment did not affect the convulsant activity of PTZ, indicating that it does not have proconvulsant properties in this...
model. This observation confirms our previous report that finasteride, at a dose much higher than used here to induce neurosteroid withdrawal, failed to affect the convulsant threshold of PTZ in mice (Kokate et al., 1999). The lack of effect of finasteride on seizure threshold in control animals suggests that basal neurosteroid levels do not have a substantial influence on seizure susceptibility. However, alterations in neurosteroid levels during the estrous cycle may affect seizure susceptibility in some models (Finn and Gee, 1994; Frye et al., 1998).

A variety of considerations indicate that the enhanced activity of ganaxolone in our model is specifically related to neurosteroid withdrawal and is not due to pseudopregnancy per se, to the effects of the hormone treatments used to induce pseudopregnancy, or to finasteride. Thus, pseudopregnant rats not undergoing withdrawal did not exhibit an overall enhanced sensitivity to ganaxolone. However, at high doses, ganaxolone appeared to have slightly greater potency in pseudopregnant control animals, although this effect did not reach statistical significance (Fig. 1). This enhanced activity may be due to the synergism between the high level of endogenous neurosteroid (present only in this group of animals) and the exogenously administered ganaxolone. In addition, finasteride pretreatment failed to alter the anticonvulsant potency of ganaxolone in control (not pseudopregnant) animals. Taken together, these observations permit the conclusion that allopregnanolone withdrawal, and not the pseudopregnant state or finasteride treatment, is responsible for the enhanced sensitivity to ganaxolone. Indeed, neuroactive steroids have previously been shown to have enhanced anticonvulsant activity after diazepam (Tsuda et al., 1997) and ethanol withdrawal (Devaud et al., 1996; 1998), which, like ganaxolone, act as positive allosteric modulators of GABA_A receptors. Moreover, there is a suggestion that during diestrous, when progesterone levels have fallen, allopregnanolone has increased potency as a GABA_A receptor modulator (Finn and Gee, 1993) and as an anticonvulsant against PTZ-induced seizures (Finn and Gee, 1994).

The mechanisms accounting for the enhanced anticonvulsant potency of ganaxolone after neurosteroid withdrawal were not addressed in this study. One attractive possible mechanism is that the neurosteroid sensitivity of GABA_A receptors relevant to the anticonvulsant activity of ganaxolone is enhanced after neurosteroid withdrawal. Recently, however, Smith et al. (1998) have reported that hippocampal GABA_A receptors show reduced sensitivity to allopregnanolone 24 h after withdrawal from allopregnanolone. Therefore, if changes in GABA_A receptor sensitivity do account for the present results, a distinct population must be involved.

In contrast to the enhanced sensitivity to ganaxolone, we observed a marked decrease in the anticonvulsant potency of diazepam and valproate. Our results are consistent with a recent study demonstrating a reduction in the sedative effects of the benzodiazepine lorazepam after progesterone withdrawal (Moran et al., 1998). This benzodiazepine insensitivity has been attributed to a specific increase in the expression of the a4 GABA_A receptor subunit (Smith et al., 1998). A similar benzodiazepine insensitivity has been noted after withdrawal from barbiturates and ethanol (Buck and Harris, 1990; Roca et al., 1990). In addition, attenuated benzodiazepine sensitivity has been observed clinically in patients with premenstrual syndrome (Sundström et al., 1997a,b), a condition that may be related to catamenial epilepsy. However, it remains to be determined whether women with catamenial epilepsy have reduced sensitivity to benzodiazepines. Valproate also had markedly attenuated anticonvulsant potency after neurosteroid withdrawal. Although the basis for the anticonvulsant activity of valproate is not well understood, it may act in part through effects on GABA-mediated inhibition (Rogawski and Porter, 1990). In fact, there is evidence of cross-tolerance between benzodiazepines and valproate (Gent et al., 1986). Thus, the reduced activity of diazepam and valproate may have a similar underlying basis.

In summary, the results of this study demonstrate that there is enhanced anticonvulsant sensitivity to ganaxolone during neurosteroid withdrawal, whereas the anticonvulsant activities of diazepam and valproate are reduced. There is no corresponding enhancement of the motor toxicity of ganaxolone, so its protective index is greater after neurosteroid withdrawal than under ordinary circumstances. Thus, ganaxolone could be of use in the treatment of perimenstrual catamenial epilepsy, a condition that is often resistant to other anticonvulsant therapies.

References


Buck KJ and Harris RA (1990) Benzodiazepine insensitivity has been attributed to a specific increase in the expression of the a4 GABA_A receptor subunit (Smith et al., 1998). A similar benzodiazepine insensitivity has been noted after withdrawal from barbiturates and ethanol (Buck and Harris, 1990; Roca et al., 1990). In addition, attenuated benzodiazepine sensitivity has been observed clinically in patients with premenstrual syndrome (Sundström et al., 1997a,b), a condition that may be related to catamenial epilepsy. However, it remains to be determined whether women with catamenial epilepsy have reduced sensitivity to benzodiazepines. Valproate also had markedly attenuated anticonvulsant potency after neurosteroid withdrawal. Although the basis for the anticonvulsant activity of valproate is not well understood, it may act in part through effects on GABA-mediated inhibition (Rogawski and Porter, 1990). In fact, there is evidence of cross-tolerance between benzodiazepines and valproate (Gent et al., 1986). Thus, the reduced activity of diazepam and valproate may have a similar underlying basis.

In summary, the results of this study demonstrate that there is enhanced anticonvulsant sensitivity to ganaxolone during neurosteroid withdrawal, whereas the anticonvulsant activities of diazepam and valproate are reduced. There is no corresponding enhancement of the motor toxicity of ganaxolone, so its protective index is greater after neurosteroid withdrawal than under ordinary circumstances. Thus, ganaxolone could be of use in the treatment of perimenstrual catamenial epilepsy, a condition that is often resistant to other anticonvulsant therapies.

References


Buck KJ and Harris RA (1990) Benzodiazepine insensitivity has been attributed to a specific increase in the expression of the a4 GABA_A receptor subunit (Smith et al., 1998). A similar benzodiazepine insensitivity has been noted after withdrawal from barbiturates and ethanol (Buck and Harris, 1990; Roca et al., 1990). In addition, attenuated benzodiazepine sensitivity has been observed clinically in patients with premenstrual syndrome (Sundström et al., 1997a,b), a condition that may be related to catamenial epilepsy. However, it remains to be determined whether women with catamenial epilepsy have reduced sensitivity to benzodiazepines. Valproate also had markedly attenuated anticonvulsant potency after neurosteroid withdrawal. Although the basis for the anticonvulsant activity of valproate is not well understood, it may act in part through effects on GABA-mediated inhibition (Rogawski and Porter, 1990). In fact, there is evidence of cross-tolerance between benzodiazepines and valproate (Gent et al., 1986). Thus, the reduced activity of diazepam and valproate may have a similar underlying basis.

In summary, the results of this study demonstrate that there is enhanced anticonvulsant sensitivity to ganaxolone during neurosteroid withdrawal, whereas the anticonvulsant activities of diazepam and valproate are reduced. There is no corresponding enhancement of the motor toxicity of ganaxolone, so its protective index is greater after neurosteroid withdrawal than under ordinary circumstances. Thus, ganaxolone could be of use in the treatment of perimenstrual catamenial epilepsy, a condition that is often resistant to other anticonvulsant therapies.

References


Buck KJ and Harris RA (1990) Benzodiazepine insensitivity has been attributed to a specific increase in the expression of the a4 GABA_A receptor subunit (Smith et al., 1998). A similar benzodiazepine insensitivity has been noted after withdrawal from barbiturates and ethanol (Buck and Harris, 1990; Roca et al., 1990). In addition, attenuated benzodiazepine sensitivity has been observed clinically in patients with premenstrual syndrome (Sundström et al., 1997a,b), a condition that may be related to catamenial epilepsy. However, it remains to be determined whether women with catamenial epilepsy have reduced sensitivity to benzodiazepines. Valproate also had markedly attenuated anticonvulsant potency after neurosteroid withdrawal. Although the basis for the anticonvulsant activity of valproate is not well understood, it may act in part through effects on GABA-mediated inhibition (Rogawski and Porter, 1990). In fact, there is evidence of cross-tolerance between benzodiazepines and valproate (Gent et al., 1986). Thus, the reduced activity of diazepam and valproate may have a similar underlying basis.

In summary, the results of this study demonstrate that there is enhanced anticonvulsant sensitivity to ganaxolone during neurosteroid withdrawal, whereas the anticonvulsant activities of diazepam and valproate are reduced. There is no corresponding enhancement of the motor toxicity of ganaxolone, so its protective index is greater after neurosteroid withdrawal than under ordinary circumstances. Thus, ganaxolone could be of use in the treatment of perimenstrual catamenial epilepsy, a condition that is often resistant to other anticonvulsant therapies.
Sundstrom I, Nyberg S and Backstrom T (1997b) Patients with premenstrual syndrome have reduced sensitivity to midazolam compared to control subjects. *Psychoneuroendocrinology* **22**:370–381.

Send reprint requests to: Michael A. Rogawski, M.D., Ph.D., National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Dr., Room 5N-250, MSC 1408, Bethesda, MD 20892-1408. E-mail: rogawski@nih.gov