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Review Article

Ganaxolone: a prospective overview

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Abstract

Ganaxolone is a synthetic analogue of the endogenous neurosteroid allopregnanolone, a metabolite of progesterone. Like allopregnanolone, ganaxolone is a potent positive allosteric modulator of γ-aminobutyric acid type A ($GABA_A$) receptors. Ganaxolone has robust anticonvulsant effects in a variety of animal models of epilepsy, is orally active and lacks hormonal side effects. Unlike diazepam, anticonvulsant tolerance does not develop to ganaxolone following chronic therapy. Recent preclinical studies suggest that ganaxolone is a particularly promising treatment for catamenial epilepsy, a menstrual cycle-related seizure disorder characterized by an increase in seizures at the time of menstruation. Preliminary evidence of the efficacy of ganaxolone in the treatment of epilepsy is encouraging. In general, ganaxolone has a favorable safety profile. The most frequently reported side effect is somnolence, which occurs with an acceptable therapeutic index. Ganaxolone has demonstrated significant clinical efficacy in suppressing complex partial seizures. Two open-label trials of ganaxolone in infantile spasms have been reported with indications of efficacy in both cases. Ganaxolone has enhanced potency in an animal model of catamenial epilepsy, and there is promising preliminary evidence for the efficacy of ganaxolone 'pulse therapy' for catamenial seizures in women. In addition, since premenstrual syndrome (PMS) is associated with allopregnanolone deficiency, ganaxolone may also have utility in the management of PMS. As a novel $GABA_A$ receptor modulator with unique, broad-spectrum protective efficacy, ganaxolone may have additional therapeutic potential in alcohol and cocaine withdrawal seizures, as well as in the treatment of anxiety and other mood disorders.

Introduction

Epilepsy, one of the most common neurological disorders in humans and animals, is characterized by the repeated occurrence of uncontrolled seizures. Epilepsy affects an estimated 2.5 million people of all ages and backgrounds in the United States and 50 million worldwide (1). Antiepileptic drugs are the mainstay for the treatment of epilepsy, and generally suppress seizure occurrence (Table I). None of these agents, however, meets the ideal characteristics of an antiepileptic drug, *i.e.*, protecting against seizures without inducing adverse effects that impair the patient's quality of life. Despite many advances in epilepsy research, the pharmacotherapy of epilepsy remains largely empirical due to the lack of understanding of the underlying neurochemistry and pathology. Moreover, nearly 30% of people with epilepsy have intractable seizures that do not respond to even the best available treatment. These statistics make it clear that novel treatments are desperately needed for the treatment and prevention of epilepsy.

Ganaxolone (CCD-1042) is a synthetic neuroactive steroid that was originally discovered at CoCensys for the treatment of epilepsy (2, 3). It was acquired by Purdue Pharma in 1999 for further clinical evaluation. Ganaxolone was developed as a result of an elegant series of studies by Gee *et al.*, who demonstrated that endogenously occurring metabolites of progesterone, such as allopregnanolone and pregnanolone, are powerful anticonvulsants in animal models of epilepsy (4, 5).

The sedative-anesthetic activity of steroid hormones was first described by the physiologist Hans Selye (6, 7), which was followed by the discovery of alphaxolone (a component of Althesin®) as an intravenous anesthetic by Glaxo in the early 1970s (8, 9). These studies led to the discovery of neuroactive steroids, steroids synthesized in the central nervous system and their synthetic analogues which rapidly alter neural excitability, as promising therapeutic agents (10-12). Allopregnanolone is a neurosteroid

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Table I: Drugs used for the treatment of epilepsy.

Drug	Mechanism of action	Efficacy
Standard drugs:		
Carbamazepine (Tegretol)	Na^+ channel blocker	Broad spectrum
Clonazepam (Klonopin)	$GABA_A$ receptor modulator	Broad spectrum/status epilepticus
Clorazepate (Tranxene)	$GABA_A$ receptor modulator	Partial/alcohol withdrawal seizures
Diazepam (Valium)	$GABA_A$ receptor modulator	Status epilepticus/febrile seizures
Divalproex sodium (Depakote)	GABA synthesis modulator	Broad spectrum
Ethosuximide (Zarontin)	T-type Ca^{2+} channel blocker	Absence seizures
Ethytoin (Peganone)	Na^+ channel blocker	Partial/generalized seizures
Lorazepam (Ativan)	$GABA_A$ receptor modulator	Status epilepticus/alcohol withdrawal seizures
Methsuximide (Celontin)	T-type Ca^{2+} channel blocker	Absence seizures
Nitrazepam (Mogadon)	$GABA_A$ receptor modulator	Absence seizures/infantile spasms
Phenobarbital (Gardinal)	$GABA_A$ receptor modulator	Partial/generalized seizures/status epilepticus
Phenytoin (Dilantin)	Na^+ channel blocker	Partial/generalized seizures
Primidone (Mysoline)	$GABA_A$ receptor modulator	Partial/generalized seizures
Valproic acid (Depakene)	GABA synthesis modulator/ Na^+ blocker	Broad spectrum
Newer drugs:		
Acetazolamide (Diamox)	Carbonic anhydrase inhibitor	Partial/generalized seizures
Felbamate (Felbatol)	Na^+, Ca^{2+} and NMDA blocker	Broad spectrum/LGS
Fosphenytoin (Cerebyx)	Prodrug of phenytoin	Status epilepticus
Gabapentin (Neurontin)	GABA modulator/Ca^{2+} channel blocker	Partial seizures (add-on)
Lamotrigine (Lamictal)	Na^+ channel blocker	Broad spectrum/LGS
Levetiracetam (Keppra)	Ca^{2+}, $GABA_A$ receptor modulator	Partial/generalized seizures
Oxcarbazepine (Trileptal)	Na^+, Ca^{2+} channel blocker	Partial/generalized seizures
Tiagabine (Gabitril)	GABA uptake inhibitor	Partial seizures (add-on)
Topiramate (Topamax)	Na^+,GABA, AMPA channel modulator	Broad spectrum
Vigabatrin (Sabril)	GABA transaminase inhibitor	Partial seizures/infantile spasms
Zonisamide (Zonegran)	Na^+, Ca^{2+} channel blocker	Partial/generalized seizures

Broad spectrum = partial/generalized, absence and myoclonic seizures; LGS = Lennox-Gastaut syndrome.

synthesized from progesterone in peripheral tissues and also in the brain (Fig. 1) (13, 14). Neurosteroids are steroids that are synthesized in the brain from either cholesterol or steroid hormone precursors and that rapidly alter neural excitability by modulating membrane receptors (15). Allopregnanolone and related neuroactive steroids are potent positive allosteric modulators of the $GABA_A$ receptor (16-20), a subtype receptor for the neurotransmitter GABA which mediates the bulk of synaptic inhibition in the brain, and hence $GABA_A$ receptor-modulating neuroactive steroids represent novel protective agents against epileptic seizures (5, 21).

Allopregnanolone and pregnanolone possess powerful anticonvulsant effects (4, 22-26). However, these naturally occurring neuroactive steroids are orally inactive because of first-pass metabolic degradation in the liver, and may also be converted to metabolites with undesired classical progestational activity (27). For example, the 3-hydroxyl group of allopregnanolone may undergo oxidation to a ketone, restoring activity at steroid hormone receptors (28). In addition, allopregnanolone and pregnanolone have a very short half-life ($t_{1/2}$ = 15-20 min). Ganaxolone, the synthetic 3-methyl analogue of allopregnanolone (Fig. 2), overcomes these limitations. The 3β-methyl substituent minimizes metabolism at the 3α-OH group, rendering ganaxolone orally active and preventing conversion to the hormonally active 3-keto form, and it therefore lacks hormonal side effects.

Mechanism of action

Ganaxolone has a novel mode of action. Like allopregnanolone, ganaxolone binds to postsynaptic $GABA_A$ receptors (3) at a site referred to as the neurosteroid or epalon site that is thought to be distinct from the recognition sites for GABA, benzodiazepines and barbiturates (Fig. 3) (20, 29-32). $GABA_A$ receptors are ligand-gated Cl^- channels typically assembled from 3 different subunits, where each subunit exists in multiple isoforms (33, 34). Current data suggest that the mammalian brain contains at least 15 different subunit combinations (receptor subtypes); the most abundant being α1β2γ2, α2β3γ2 and α3β3γ2 (35, 36).

Electrophysiological studies in *Xenopus* oocytes expressing human $GABA_A$ receptors (*e.g.*, α1β2γ2) demonstrated that ganaxolone is a potent positive allosteric modulator of $GABA_A$ receptor function, with an EC_{50} of 94-213 nM (3). As predicted for a positive allosteric $GABA_A$ modulator, ganaxolone (80-125 nM) enhances the specific binding of [^{3}H]-flunitrazepam, an agonist at the benzodiazepine binding site of $GABA_A$ receptors, and [^{3}H]-muscimol, a specific GABA-site $GABA_A$ receptor agonist, and inhibits the binding of [^{35}S]-*tert*-butylbicycloorthobenzoate (TBPS), a cage convulsant and noncompetitive $GABA_A$ receptor antagonist. The subtype selectivity profile for ganaxolone is similar to other neuroactive steroids, which generally do not show

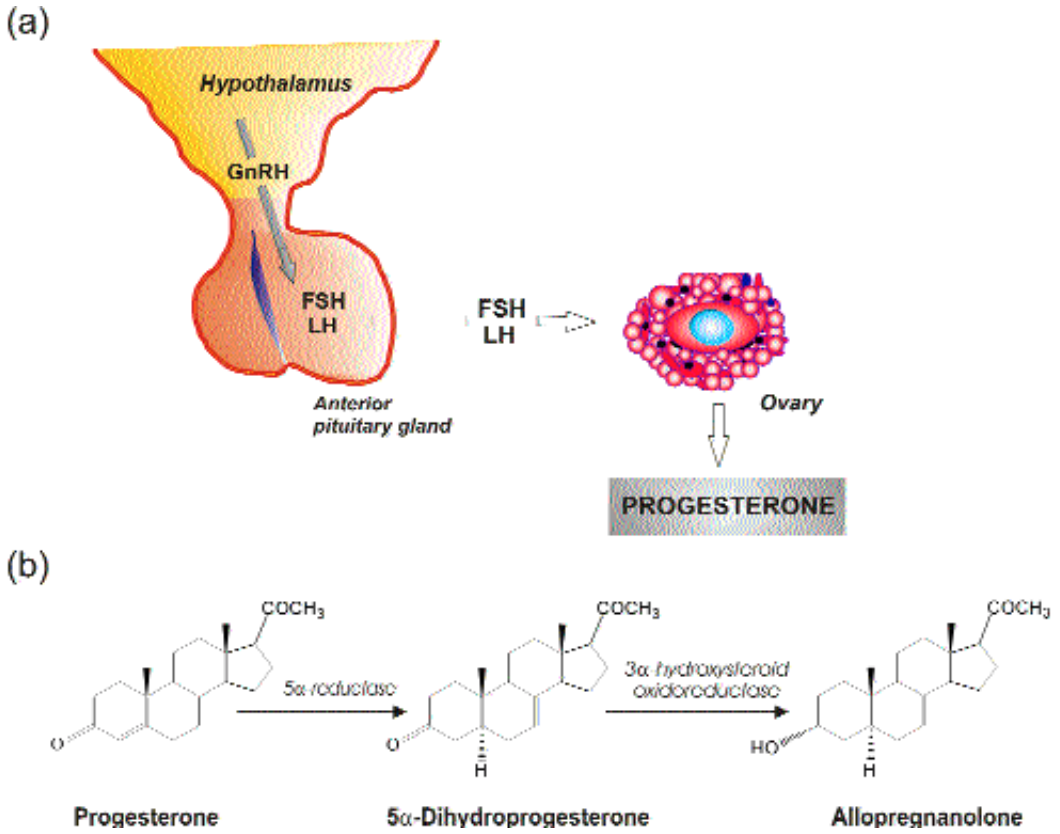

Fig. 1. Overview of progesterone secretion and allopregnanolone synthesis. (a) Progesterone is secreted by the corpus luteum in the ovaries. Gonadotropin-releasing hormone (GnRH), a decapeptide synthesized in the hypothalamus, stimulates the synthesis and release of gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the posterior pituitary gland in an intermittent or pulsatile manner. FSH and LH stimulate the growth and development of ovarian follicles, inducing ovulation and the production of progesterone and estrogens. Progesterone modifies the release of GnRH and gonadotropins through negative feedback on the hypothalamic-pituitary-ovarian axis. (b) The neuroactive steroid allopregnanolone is synthesized from progesterone by two sequential A-ring reductions. The 5α-reductase enzyme first converts progesterone to the intermediate 5α-dihydroprogesterone, which is then further reduced by 3α-hydroxysteroid oxidoreductase to form allopregnanolone. The conversion of progesterone to allopregnanolone occurs both in peripheral tissues and in the brain. However, peripherally synthesized allopregnanolone readily accumulates and achieves rapid equilibrium in the brain. In addition, a small quantity of allopregnanolone is also produced locally within the brain from cholesterol, which seems to be independent of its secretion from ovaries and adrenal cortex.

Fig. 2. Chemical structures of ganaxolone and allopregnanolone. Ganaxolone is the 3β-methyl derivative of allopregnanolone (3α-hydroxy-5α-pregnan-20-one).

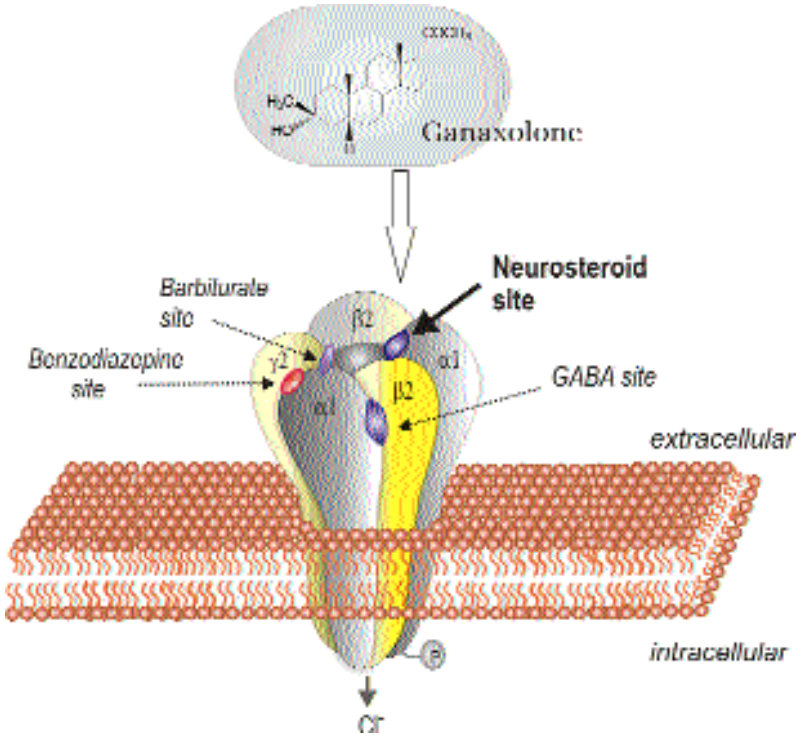

Fig. 3. Ganaxolone modulation of the $GABA_A$ receptor. Like allopregnanolone**,** the binding site for ganaxolone is thought to be at the neurosteroid site, which is distinct from sites for GABA, benzodiazepines and barbiturates. Structurally, $GABA_A$ receptors are believed to be pentameric with 5 protein subunits that form the chloride ion channel pore. There are 7 different classes of subunits, some of which have multiple homologous variants (α1-6, β1-3, γ1-3, σ1-3, δ, ε, θ); most $GABA_A$ receptors are believed to be composed of α, β and γ subunits. GABA activates the opening of an ion channel that gates chloride ions, in most cases causing hyperpolarization of neurons and reductions in neuronal excitability. Ganaxolone potentiation of $GABA_A$ receptor function almost certainly underlies its protective effect against seizures.

pronounced selectivity for different subunit combinations in recombinant expression systems (20, 37).

Early studies suggested that the δ-subunit attenuated sensitivity to neuroactive steroids (38). However, subsequent work indicated that other δ-subunit-containing combinations actually have increased sensitivity to neuroactive steroids (39). In [^{35}S]-*tert*-TBPS binding studies, ganaxolone modulates α1-3 & 5β2γ2 subunit combinations with high potency, but appears to be weaker on α4β2γ2 and α6β2γ2 (J.E. Hawkinson and S. Espitia, unpublished results).

At relatively high concentrations (10 μM), ganaxolone, in the absence of GABA, directly activates the $GABA_A$ receptor channel function, being comparable in potency and efficacy to endogenous neuroactive steroids like allopregnanolone and THDOC in cultured hippocampal neurons (21, 40). However, the level of direct activation, particularly when using native $GABA_A$ receptors, is appreciably smaller than that produced by high concentrations of barbiturates (E.R. Whittemore and R.M. Woodward, unpublished results).

In terms of single-channel recordings, endogenous neuroactive steroids increase both channel opening frequency and open channel duration, which further distinguishes the molecular mechanism from benzodiazepines and barbiturates (33, 41, 42). Moreover, long-term exposure of neurons to ganaxolone does not affect $GABA_A$ receptor plasticity or functional properties *in vitro* (43).

In vivo studies using quantitative real-time TaqMan PCR analysis showed that chronic ganaxolone does not significantly change the expression levels of $GABA_A$ receptor α1 and α2 subunits (D.S. Reddy, unpublished results). Ganaxolone does not bind to classical steroid hormone receptors, and has little or no interaction with other neurotransmitter receptors tested, including excitatory amino acid, $GABA_B$, peptide and monoamine receptors (3). Thus, ganaxolone appears to be a specific positive modulator of $GABA_A$ receptor function in the mammalian brain.

Anticonvulsant profile

Pharmacological studies indicate that ganaxolone is a potent, broad-spectrum anticonvulsant. Ganaxolone elevates the clonic seizure threshold to intravenous infusions of pentylenetetrazol (PTZ) in mice (3) and rats (D.S. Reddy, unpublished data). Like allopregnanolone and several other $GABA_A$ receptor positive modulators (4, 44), ganaxolone protects against corneal kindling seizures

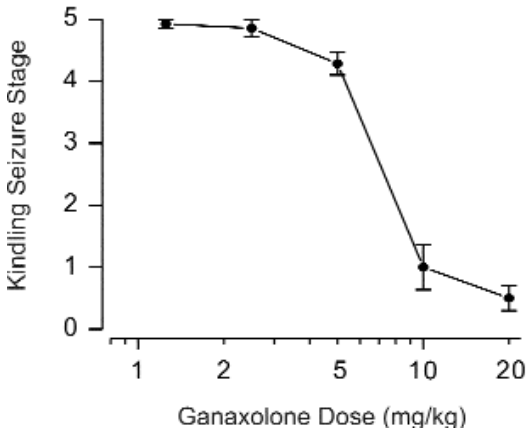

Fig. 4. Anticonvulsant activity of ganaxolone in an amygdala kindling model of epilepsy. The dose-response relationship for antiseizure activity of ganaxolone (1-20 mg/kg s.c.) was tested 15 min after administration of ganaxolone to fully kindled mice. Before testing ganaxolone, animals were stimulated daily via an implanted electrode in the amygdala until a stage 5 seizure was elicited on 3 consecutive days. Behavioral seizures were scored as per the Racine scale between stage 1 (least severe) and stage 5 (most severe) of seizure expression. Ganaxolone at a dose of 10 mg/kg completely suppressed the occurrence of seizures induced by kindling stimuli in fully kindled mice. Each point represents the mean ± SEM of data from 6-8 animals. D.S. Reddy, unpublished data.

Table II: Anticonvulsant profile of ganaxolone in mouse models of epilepsy.

Seizure model	ED_{50} value (mg/kg i.p./s.c.)	Ref.
Pentylenetetrazol	4.3 (2.9-6.9)	3, 45
Pentylenetetrazol	3.5 (2.06-5.82)*	47, 49
Bicuculline	4.6 (3.2-6.8)	3
TBPS	11.7 (8.8-15.7)	3
Aminophylline	11.5 (8.1-16.3)	3
Flurothyl	~ 5 (ND)	48
Cocaine	7.8 (3.6-17)	45
Corneal kindling	4.5 (4.0-5.1)*	45
Amygdala kindling	~ 6.5 (ND)	Fig. 4
Pentylenetetrazol kindling	4.1 (2.7-6.4)	46
Cocaine kindling	~17 (ND)	50
Strychnine	> 40 (ND)	3
NMDA	> 30 (ND)	3
Maximal electroshock	29.7 (25.3-34.8)	3
γ-Hydroxybutyrate	Pro (ND)	51
Rotarod (TD_{50}, p.o.)	33.4 (30.9-39.4)	3

*ED_{50} value in rats; TBPS = *tert*-butylbicycloorthobenzoate; Pro = proconvulsant; ND = not determined. ED_{50} values were determined according to the Litchfield and Wilcoxon procedure. Numbers in parentheses are 95% confidence intervals.

and seizures induced in animals by $GABA_A$ receptor antagonists such as PTZ, bicuculline and TBPS (3, 26, 45-47). Ganaxolone has protective effects against flurothyl-induced seizures in all age groups tested, although its effects are more prominent in younger age groups (48). In addition, ganaxolone exhibits anticonvulsant and antiepileptogenic activity in electrical and chemical kindling models (3, 46). The dose-response relationship of ganaxolone protection against amygdala kindling seizures is illustrated in Figure 4. The doses of ganaxolone producing 50% seizure protection (ED_{50}) in various seizure models are summarized in Table II. The estimated plasma concentrations of ganaxolone at ED_{50} doses are 500-750 ng/ml in rats (47, 49).

Ganaxolone is highly effective in suppressing the seizures induced by cocaine treatment (45, 50). At very high doses, ganaxolone also protects mice against maximal electroshock (MES)-induced seizures and causes motor incoordination (ataxia) in the rotarod test (3, 47). However, like many GABA enhancers, ganaxolone exacerbates seizures in animal models of absence epilepsy (51). Ganaxolone is inactive against tonic seizures induced by the glycine antagonist strychnine and limbic seizures induced by the glutamate receptor agonist NMDA. In mice, the potency ranking of ganaxolone is PTZ > bicuculline > kindling > cocaine > aminophylline > TBPS > MES (Table II). The protective index (TD_{50} in rotarod test/ED_{50} in seizure test) is 2-8, which is comparable or superior to that of diazepam and sodium valproate. In addition, ganaxolone has moderate protective efficacy against neurological disruptions in a rat model of cerebral hematoma (52).

Benzodiazepines such as diazepam and clonazepam are effective antiepileptic drugs, but their clinical usefulness is severely limited because of tolerance to their protective effects following long-term therapy. Interestingly, tolerance does not develop to the anticonvulsant activity of ganaxolone during repeated dosing for 7 days (47). This is consistent with a similar lack of anticonvulsant tolerance to chronic pregnanolone, an isomer of allopregnanolone and $GABA_A$ receptor-modulating neuroactive steroid (53). Overall, these studies suggest that ganaxolone has a unique anticonvulsant profile and hence may have utility in the treatment of a broad range of seizure types.

Pharmacokinetics and metabolism

The pharmacokinetics of ganaxolone in rats, monkeys and dogs are summarized in Table III. Ganaxolone is rapidly absorbed after oral and systemic administration in animals (47, 54) and is rapidly distributed throughout the body. Aqueous solutions/suspensions of ganaxolone prepared using a β-cyclodextrin vehicle are much more efficiently absorbed after systemic administration. Ganaxolone has an acceptable half-life in rodents and primates ($t_{1/2}$ = 1.5-5 h). It has a large apparent volume of distribution (V_d = 3-4 l/kg), indicating that it is well distributed in the tissues. Moreover, plasma ganaxolone time profile determinations indicate that the pharmacokinetic properties of ganaxolone do not change significantly after chronic 7-day treatment (Table IV) (47).

Table III: Pharmacokinetics of ganaxolone in animals after a dose of 10 mg/kg p.o.

Parameter	Rat	Monkey	Dog
C_{max} (ng/ml)	37 ± 36	28 ± 14	1109 ± 243
t_{max} (h)*	1.0 (1-2)	5.0 (2-6)	0.8 (0.5-1)
$t_{1/2}$ (h)	3.1 ± 1.8	4.9 ± 1.0	25.0 ± 5.7
$AUC_{(0-\infty)}$ (ng/h/ml)	126 ± 124	232 ± 92	12,875 ± 5,976

*Expressed as median and range. Pharmacokinetic parameters were determined by standard model-independent methods based on the plasma concentration-time data. Values represent means ± standard deviation. Data from Ref. 54.

Table IV: Pharmacokinetics of ganaxolone (7 mg/kg s.c.) after acute and chronic (7 days, b.i.d.) treatment in rats.

Parameter	Acute	Chronic
K_a (h^{-1})	1.6 ± 0.6	0.7 ± 0.4
K_e (h^{-1})	0.60 ± 0.03	0.40 ± 0.10
C_p' (t=0) (mg/l)	2.23 ± 0.20	2.12 ± 0.23
C_{max} (mg/l)	1.50 ± 0.00	1.46 ± 0.03
$t_{1/2}$ (h)	1.3 ± 0.1	1.9 ± 0.3
t_{max} (h)	0.75 ± 0.15	0.75 ± 0.15
$AUC_{(0-\infty)}$ (mg-h/l)	3.45 ± 0.19	4.73 ± 0.51
V_d /F (l/kg)	3.27 ± 0.52	4.02 ± 0.30

K_a and K_e = absorption and elimination rate constants, respectively; C_p' (t=0) = convolution of the serum concentration at time 0; C_{max} = maximum serum concentration at time t_{max}; AUC = area under the curve (represents total drug absorbed); V_d = apparent volume of distribution; F = fraction absorbed into plasma. A 2-compartment model was used to describe the plasma concentration-time profile of ganaxolone after s.c. administration. Values are means ± S.E.M. Data from Ref. 47.

Brain concentrations of neuroactive steroids are normally expected to increase in parallel with plasma levels (55-57). Since ganaxolone is highly lipophilic and can readily cross the blood-brain barrier, it is expected to establish a rapid equilibrium between plasma and brain concentrations. The apparent temporal dissociation between the extent of seizure protection and plasma ganaxolone levels at early times after ganaxolone administration (47) suggests that it might have a tendency to accumulate in the brain. However, data from preclinical pharmacokinetic studies of ganaxolone do not support this possibility. Ganaxolone concentrations were determined in plasma and brain following ganaxolone administration in rats and regression lines were constructed for dose and actual concentration. Plasma and brain concentrations of ganaxolone clearly paralleled each other (r=0.986) after ganaxolone treatment (D.S. Reddy, unpublished results), indicating that ganaxolone is rapidly distributed without substantial accumulation in the brain.

Ganaxolone is orally active and adequate blood levels can be maintained in human subjects with b.i.d. or t.i.d. dosing (58). The pharmacokinetic properties of ganaxolone in human subjects are given in Table V. Like many drugs, ganaxolone displays high plasma protein binding (> 90%). In single-dose studies, pharmacokinetic analyses show a linear and dose-proportional increase in the area under the curve (AUC) over the dose range 50-800 mg, with a less-than-proportional increase in AUC and C_{max} over the range 900-1600 mg (59). Peak plasma levels are reached within 0.5-0.6 h and decline biexponentially with an apparent distribution half-life of 2-9 h, followed by a terminal half-life of 37-70 h. Following daily dosing over 10-14 days, the disposition of ganaxolone was not altered and accumulation was not observed (Table V). Ganaxolone pharmacokinetics also do not show gender differences. The elimination of ganaxolone involves the biliary and urinary systems.

Although it has a relatively short half-life (3-6 h), ganaxolone has linear kinetics and exhibits no interactions with other tested antiepileptic drugs (59). Like other steroids, the metabolism of ganaxolone is complex. The main metabolic route for ganaxolone is 16β-hydroxylation by CYP3A4, an isozyme of cytochrome P-450 that is involved in the biotransformation of several steroids and benzodiazepines. Thus, drugs or substances that inhibit CYP3A4 (*e.g.*, ketoconazole or grapefruit juice) are expected to decrease ganaxolone metabolism. There is no evidence for microsomal enzyme induction by ganaxolone and it would therefore be unlikely for chronic ganaxolone to affect the metabolism of diazepam or other antiepileptic drugs.

Side effects and safety

Ganaxolone treatment produces dose-dependent sedation in animals, which is consistent with its

Table V: Pharmacokinetic profile of ganaxolone after single and multiple (14 days, q.d.) oral dosing in humans.

Parameter	Single dose	Multiple dose	Single dose	Multiple dose
Dose	*200 mg/kg*	*200 mg/kg*	*500 mg/kg*	*500 mg/kg*
C_{max} (ng/ml)	75.58 ± 6.14	106.23 ± 9.53	285.55 ± 36.90	376.03 ± 39.22
t_{max} (h)*	2.75 (2.0-3.0)	2.25 (1.5-3.0)	2.25 (1.5-5.9)	2.5 (2.0-5.0)
$t_{1/2}$ (h)	39.1 ± 9.8	65.1 ± 18.1	38.1 ± 6.8	37.7 ± 9.6
$AUC_{(0-\infty)}$ (ng/h/ml)	977.9 ± 69.5	1,093.1 ± 148.1	2,639.3 ± 294.9	3,103.0 ± 497.9

*Median (range); C_{max} = maximum serum concentration at time t_{max}; AUC = area under the curve. Descriptive pharmacokinetic analysis was performed by model-independent methods based on the plasma concentration-time data. Values are means ± S.D. Data from Ref. 59.

GABAergic actions (3, 60). Although ganaxolone is extensively metabolized, the potentially hormonally active 3-keto derivative is not formed. There is no evidence that ganaxolone is teratogenic or causes other systemic toxicity following chronic administration. This is consistent with ganaxolone being a very close structural analogue of an endogenous neuromodulator. Akin to allopregnanolone and pregnanolone (61), ganaxolone appears to have a reduced propensity for pharmacodynamic interaction with alcohol in the rotarod test (TD_{50} ganaxolone = 5.6 mg/kg; TD_{50} ganaxolone + ethanol = 5 mg/kg). However, recent *in vitro* studies suggest that there is an interaction between endogenous neuroactive steroids and ethanol at the molecular level (62). Although there are no specific data for ganaxolone, another synthetic neuroactive steroid (CCD-3693) moderately impaired cognitive function in the passive avoidance model of learning and memory in the same dose range that produced sedation and ataxia (63).

More than 500 subjects have received ganaxolone in various formulations, doses and dosing regimens (59, 64, 65) and the safety and tolerability in humans have been impressive (58). As predicted by animal studies, the dose-limiting side effect is generally sedation, an effect expected for $GABA_A$ receptor modulation. Reports of adverse events have included nausea, diarrhea, flatulence, abdominal pain, lightheadedness, stupor, tiredness and headache. Most were mild in severity and resolved spontaneously. No life-threatening adverse events were observed in any of the clinical studies. Most adverse events were reported at ganaxolone doses of 800 mg or more. Although there is no clear linear relationship between ganaxolone dose and plasma levels at these high doses, concentrations of 300 ng/ml of ganaxolone appear to be the threshold for a higher incidence of CNS side effects such as sedation and somnolence.

In a multicenter, open-label, add-on trial of ganaxolone in 20 children with refractory infantile spasms, the most common adverse events were somnolence and diarrhea (25%), constipation, nervousness and somnolence (15%), and previously unseen tonic-clonic seizures (10%) which were possibly related to ganaxolone (65). In a double-blind, randomized, placebo-controlled clinical trial in 52 adult patients withdrawn from concomitant anticonvulsant medication during presurgical evaluation, ganaxolone was well tolerated, with mild to moderate CNS-related side effects (64). Overall, 19 patients in each treatment group experienced adverse events, with 47 events reported for patients who received ganaxolone and 38 events reported for patients who received placebo. The most frequently reported side effect was dizziness. One patient experienced severe agitation and depression after 1 day of treatment at 500 mg t.i.d. ganaxolone.

Clinical efficacy in epilepsy

To date, ganaxolone has been tested in several phase II clinical trials in the U.S. and Europe for three indications: treatment of adults with complex partial epilepsy, treatment of children with epilepsy refractory to other treatments, and acute treatment of migraine headache. In pilot studies, ganaxolone was also given to 2 women with catamenial epilepsy. In these various studies, ganaxolone was given in oral dosage forms including an oral suspension (25 or 50 mg/ml) and tablets (250, 300 or 400 mg) formulated using pharmaceutical-grade β-cyclodextrin.

Complex partial seizures

Ganaxolone has significant efficacy in treating adult patients with refractory partial and generalized seizures (58). A recent double-blind, randomized, placebo-controlled trial in 52 patients withdrawn from concomitant anticonvulsant medication during presurgical evaluation reported that ganaxolone was well tolerated and had significant efficacy (64). The inpatient monotherapy trial was designed to rapidly evaluate the antiepileptic efficacy of ganaxolone. Eligible subjects included patients who had undergone evaluation for surgical intervention of their seizures. Patients were randomized to receive either ganaxolone or placebo (1:1 ratio). Ganaxolone was administered at 500 mg t.i.d. on day 1 and 625 mg t.i.d. on the subsequent 7 days of the study period. The primary efficacy measure was duration of treatment before withdrawal from the trial. Patients were withdrawn from the trial at the occurrence of any of the following: 4 seizures of any type (excluding single partial seizures), 3 generalized tonic-clonic seizures or status epilepticus. Kaplan-Meier curves depicted a clear separation between treatment groups. Thus, while 50% of patients treated with ganaxolone completed the trial, 75% of patients treated with placebo withdrew before trial completion. Covariate analyses indicated a significant treatment effect on survival time in men ($p < 0.05$). *Post hoc* analyses focusing on patients who completed the entire study revealed a significant difference ($p < 0.05$) between treatment groups. These results provide preliminary evidence for the antiepileptic efficacy of ganaxolone monotherapy. However, as ganaxolone was only administered during an 8-day period, longer term studies in larger patient groups are needed to clearly define the efficacy of ganaxolone in complex partial seizures.

Infantile spasms

Infantile spasms is an epilepsy syndrome with several distinctive features, including age specificity during infancy, characteristic semiology (epileptic spasms), specific electroencephalographic (EEG) patterns (interictal hypsarrhythmia and ictal voltage suppression), and responsiveness to adrenocorticotropic hormone (ACTH). Infantile spasms, also known as West's syndrome, usually begin in the first year of life and affect 1 in every 2,000-4,000 infants in the United States, and 3 per 10,000 infants worldwide. Infantile spasms are often associated

with a focal or diffuse encephalopathy and can result in severe neurodevelopmental delay and retardation. Although the syndrome was identified 160 years ago, it is still not fully understood.

Because of the multiple etiologies associated with infantile spasms, evaluation and treatment of the disease are complex, and to date, there are no FDA-approved drugs for the treatment of infantile spasms. The seizures respond poorly to conventional anticonvulsants (66). A majority of children (~50%) will develop epilepsy later in life (67). There is no effective nonhormonal drug for infantile spasms, perhaps due to these clinically unique features that are specific for the developing human brain. Adrenocorticotropic hormone is the drug of choice for the treatment of infantile spasms (68) but is associated with serious Cushing's syndrome-like adverse effects. Infantile spasms respond to vigabatrin, but it produces serious retinopathy (69). Since ACTH stimulates adrenal deoxycorticosterone synthesis, which in turn increases levels of the neuroactive steroid THDOC, neuroactive steroids could partially contribute to the protective effects of ACTH in infantile spasms (70). Deoxycorticosterone and its metabolite THDOC have protective effects against seizures induced by $GABA_A$ receptor antagonists and amygdala kindling (70). Moreover, THDOC is also a potent allosteric modulator of the $GABA_A$ receptor. Thus, synthetic neuroactive steroids are proposed as a new, nonhormonal therapeutic approach to infantile spasms.

In 1994, ganaxolone received FDA orphan drug designation for the treatment of infantile spasms. Recent multicenter clinical trials of ganaxolone support a role for neuroactive steroids in the treatment of infantile spasms. Two open-label trials of ganaxolone in infantile spasms have been reported with indications of efficacy in both cases. Overall, approximately one-third of 79 patients aged 6 months to 15 years with highly refractory infantile spasms showed substantial (> 50%) reductions in spasm frequency, with a few subjects becoming free of spasms (58). Detailed information has been provided on 15 children with active refractory infantile spasms who were treated with ganaxolone according to an escalating-dose schedule (65). Many of the children had previously been treated with ACTH or vigabatrin, and all but 1 were taking conventional antiepileptic drugs throughout the ganaxolone trial. During a 2-month ganaxolone maintenance period, 5 of these children experienced a > 50% decrease in spasm frequency (1 became spasm-free), 5 had a 25-50% reduction and the other 5 did not respond. For the high responders, doses ranged from 18 to 36 mg/kg/day, with serum concentrations in the range of 5.0-51.6 ng/ml (15-155 nM).

In an outpatient trial, 64 children aged 6 months to 15 years (44 in France and 20 in the U.S.) received ganaxolone on an entirely outpatient basis (58). Initial reports indicate that ganaxolone is well tolerated and about 30% of the highly refractory patients showed a significant decrease (> 50%) in seizure frequency during ganaxolone treatment. Thirteen patients continued ganaxolone therapy for more than 1 year. Adverse events reported include 2 cases of status epilepticus and 1 case of tachycardia that was observed following ganaxolone overdose.

The ganaxolone levels in children with infantile spasms (15-155 nM) are within the range of those that potentiate recombinant $GABA_A$ receptors in whole-cell patch-clamp studies (3, 43). However, they are substantially lower than the threshold concentrations that are protective in the rat PTZ seizure model (750-950 ng/ml) (47, 49), indicating that human infantile spasms may be exquisitely sensitive to neuroactive steroids. Again, the most common ganaxolone-related adverse events were somnolence and diarrhea (65). This study is particularly encouraging because, although the subjects were refractory to multiple medications, ganaxolone appeared to produce a robust decrease in spasm frequency. Thus, appropriately controlled trials are warranted to confirm the efficacy of ganaxolone. If such trials are consistent with the open study results, this will further validate the GABAergic synapse as a key therapeutic target for drugs aimed at treating infantile spasms and other severe developmental epilepsies.

Additional potential therapeutic uses

Catamenial epilepsy

Women with epilepsy often report an increase in seizures at the time of menstruation. This condition, referred to as catamenial epilepsy, occurs in about 70% of women with epilepsy (71-73) and is characterized by monthly epileptic seizures during a 7-day perimenstrual period (74, 75). At present, there is no specific treatment for catamenial epilepsy. The molecular mechanisms involved in the pathophysiology of catamenial epilepsy are not well understood. Progesterone appears to play a vital role in women with epilepsy and has long been known to have antiseizure activity in animal models and in clinical studies (22, 24, 76-79). In many women with epilepsy, natural cyclic variations in progesterone during the menstrual cycle may influence catamenial seizure exacerbation. Seizures decrease in the mid-luteal phase when serum progesterone levels are high, and increase premenstrually when progesterone levels fall and there is a decrease in the serum progesterone-to-estrogen ratio (80-83). Although the mechanisms underlying the effects of progesterone on seizure activity are not fully understood, premenstrual seizure exacerbations may be due to withdrawal of the antiseizure effects of progesterone and its pharmacologically active metabolites (84).

Progesterone-derived neuroactive steroids can clearly modulate seizure susceptibility. The antiseizure activity of progesterone appears to be mediated in part by its metabolic conversion to neuroactive steroids, particularly allopregnanolone (Fig. 1) (4, 85-87). Consistent with this idea, finasteride (Proscar®), a specific 5α-reductase inhibitor, selectively suppresses the antiseizure effects of progesterone while concomitantly blocking allopregnanolone synthesis (85, 88). Thus, progesterone actions

Table VI: Summary of drugs investigated for the treatment of catamenial seizures in women with epilepsy.

Drug	Proposed mechanism	Efficacy	Limitations	Ref.
Potassium bromide	CNS depression	Moderate	Sedation	97
Thyroxine	Thyroid hormone	Moderate	Cardiac toxicity	98
Acetazolamide	Carbonic anhydrase inhibition	Moderate	Tolerance	99, 100
Clobazam	$GABA_A$ receptor modulation	Moderate	Tolerance/sedation	101, 102
Oral contraceptives	Estrogens and progesterone	Moderate	Hormone toxicity	103, 104
Medroxyprogesterone acetate	Progesterone derivative	Moderate	Hormone toxicity	105, 106
Clomiphene	Antiestrogen	Moderate	Hormone toxicity	107
Progesterone	Neurosteroid synthesis	Effective	Hormone toxicity	78, 79, 108
Triptorelin	Synthetic GnRH analogue	Moderate	Hormonal toxicity	109
Ganaxolone	$GABA_A$ receptor modulation	Effective	Pilot study	110

on neuronal excitability appear to largely depend on its metabolic activation to allopregnanolone. Allopregnanolone deficiency or withdrawal may therefore lead to increased seizure susceptibility in women with epilepsy.

Consistent with this notion, Reddy *et al.* have shown that catamenial seizures can be partly attributed to "withdrawal" of allopregnanolone (26, 47, 89). These data fit well with clinical perimenstrual seizure patterns (Herzog *et al.,* 1997), and also progesterone withdrawal-induced seizure occurrence (90-92). However, there is still no definitive understanding of what might trigger seizure susceptibility during certain phases of the menstrual cycle, and what synaptic changes occur in catamenial epilepsy. A similar predisposition to seizures is observed upon abrupt discontinuation of benzodiazepines (93) and ethanol (94), which also have $GABA_A$ receptor positive-modulating properties.

Although the molecular basis of seizure susceptibility following neuroactive steroid withdrawal is not well understood, one can hypothesize that progesterone governs seizure activity through alteration of hippocampal $GABA_A$ receptor expression and function. For example, Smith *et al.* (90, 91) reported increased expression of the $GABA_A$ receptor α4 subunit and hyperexcitability of hippo-campal neurons. Interestingly however, there is no change in the expression of the α1-4, β1-3 and γ2 subunits in rat cerebral cortex and hippocampus during pregnancy or after delivery, which are associated with a massive decline in progesterone and allopregnanolone (95, 96).

A number of drugs and hormonal agents have been investigated for the management of catamenial seizures in women (Table VI) (97-110). Except for progesterone and ganaxolone, none of these agents offers significant protection against catamenial seizures. Although natural progesterone therapy benefits some women with catamenial epilepsy (78, 79), it may be associated with undesired hormonal side effects, including breakthrough bleeding, breast tenderness and amenorrhea. $GABA_A$ receptor-modulating neuroactive steroids, which are devoid of such hormonal actions, could provide a rational alternative approach to therapy (12). A neuroactive steroid "replacement" strategy has been evaluated as an effective and rational catamenial epilepsy therapy (26). Unexpectedly, neuroactive steroids such as allopregnanolone and THDOC showed enhanced anticonvulsant activity in a rat model of catamenial epilepsy, whereas benzodiazepines and valproate exhibited reduced anticonvulsant activity. Similarly, the anticonvulsant activity of neuroactive steroids is also enhanced during withdrawal from chronic ethanol (111, 112) and diazepam (113). These observations suggest that synthetic neuroactive steroids may represent a unique and specific treatment approach for perimenstrual catamenial seizure exacerbations due to neuroactive steroid deficiency or withdrawal.

Reddy *et al.* (49) have evaluated the potential of ganaxolone in the treatment of perimenstrual seizure exacerbations in a rat catamenial epilepsy model (Fig. 5). Like naturally occurring neuroactive steroids, the anticonvulsant potency of ganaxolone was enhanced in the period following steroid withdrawal, while the potencies of the reference anticonvulsants diazepam and valproate were reduced. Ganaxolone protects against seizures in catamenial (steroid-withdrawn) rats at plasma concentrations that are not anticonvulsant in control animals. In these rat studies, anticonvulsant tolerance did not develop when ganaxolone was dosed repeatedly for up to 1 week (the suggested duration for pulse therapy in women) (47).

A lack of tolerance to the anticonvulsant activity was also demonstrated with pregnanolone, an epimer of allopregnanolone (53). Indeed, recent clinical studies in women with epilepsy (79, 108) demonstrated no decrease in the anticonvulsant activity of chronically administered progesterone. Similarly, tolerance has not been observed to the anxiolytic and sedative effects of the synthetic neuroactive steroids alphaxolone and 3β-ethenyl-3α-hydroxy-5α-pregnan-20-one (114, 115). On the other hand, benzodiazepines such as diazepam lose activity upon chronic dosing due to the development of pharmacodynamic tolerance (116, 117). Ganaxolone may therefore avoid the problem of tolerance that severely limits the usefulness of benzodiazepines as anticonvulsants in long-term therapy.

Interestingly, chronic ganaxolone treatment leads to cross-tolerance to diazepam (47). This could further impact the clinical utility of benzodiazepines. There are fluctuations in endogenous $GABA_A$ receptor-modulating neuroactive steroids at menarche, during the menstrual cycle, in pregnancy, at menopause and under stressful

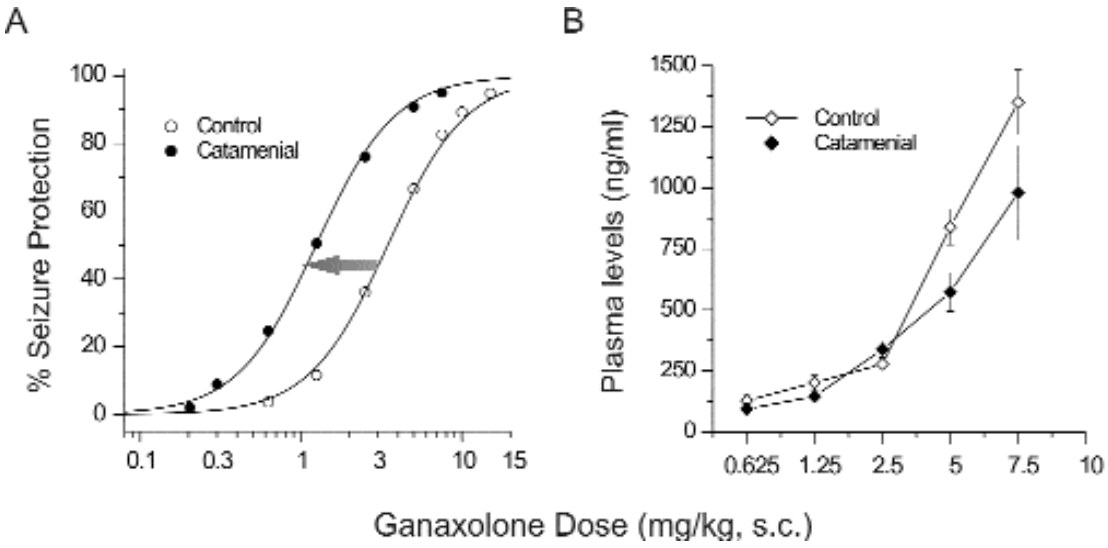

Fig. 5. Enhanced anticonvulsant activity of ganaxolone in catamenial epilepsy model. (A) Dose-response relationship for protection by ganaxolone in naïve control female rats and finasteride-treated, neuroactive steroid-withdrawn (model of catamenial epilepsy) rats. In rats with catamenial-like seizures, ganaxolone showed a 3-fold increase in the protective potency (control ED_{50} = 3.5 mg/kg; catamenial ED_{50} = 1.2 mg/kg), as reflected by a significant shift to the left of the dose-response curve for ganaxolone in catamenial animals as compared to controls. To induce catamenial seizure exacerbations, a state of persistently high serum progesterone (pseudopregnancy) was induced in 26-day-old female rats with gonadotropins, and neuroactive steroids 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. Control and experimental animals were injected with pentylenetetrazol 15 min after the indicated dose of ganaxolone. Each point represents data from 6-8 animals. (B) Plasma ganaxolone levels in rats with catamenial (pseudopregnant, neuroactive steroid-withdrawn) seizures. Values represent the mean ± SEM of levels in each group. The plasma concentrations of ganaxolone did not differ significantly in control and catamenial animals; the estimated plasma concentrations of ganaxolone producing 50% seizure protection were ~500 and ~225 ng/ml in control and withdrawn rats, respectively. Plasma samples were taken 15 min after administration of the indicated dose of ganaxolone. Ganaxolone concentrations were determined by an LC-MS method. Reproduced with permission from Ref. 49.

circumstances (15, 83, 118, 119). In these situations, persistent neuroactive steroid exposure could lead to reduced benzodiazepine sensitivity and decreased clinical efficacy. Reduced benzodiazepine sensitivity has already been observed in women with premenstrual syndrome (120). Moreover, following neuroactive steroid withdrawal, $GABA_A$ receptor currents have diminished benzodiazepine sensitivity (121) and benzodiazepines exhibit reduced sedative and anticonvulsant actions (47, 90, 91). Thus, ganaxolone might prove effective in clinical situations in which there are fluctuations in endogenous neuroactive steroid levels (*e.g.*, catamenial epilepsy and premenstrual syndrome) that reduce benzodiazepine efficacy.

Preliminary evidence of the clinical efficacy of ganaxolone in the treatment of catamenial epilepsy also supports a role for neuroactive steroids in epilepsy therapy (58). In an open-label pilot study, ganaxolone was evaluated for safety, tolerability and antiseizure efficacy in 2 women with catamenial epilepsy (110). The patients received oral ganaxolone (300 mg/day in 2 divided doses) starting on day 21 of the menstrual cycle and continuing through the third full day following the beginning of menstruation. Side effects were mild. During the 4 months of this ganaxolone pulse therapy, both patients, who were incompletely controlled with valproate and phenytoin, had a significant decrease in their catamenial seizures. Additional long-term, controlled clinical trials are again warranted to assess ganaxolone as a specific therapy in women with perimenstrual catamenial seizures.

Alcohol withdrawal seizures

There is promising evidence demonstrating that neuroactive steroids could play a role in the behavioral activity of ethanol and in ethanol withdrawal (122,123). Acute ethanol administration causes substantial increases in plasma and brain allopregnanolone concentrations that have been associated with significant protection against experimental seizure activity (124). These effects of ethanol are prevented by finasteride, indicating that they are dependent on the synthesis of neuroactive steroids. Moreover, enhanced seizure susceptibility is an important symptom of ethanol withdrawal in humans that is mimicked in laboratory animals. Devaud *et al.* have shown that allopregnanolone and THDOC are 5-15-fold more potent in protecting heightened seizure susceptibility following withdrawal from chronic ethanol exposure (111, 112).

Conversely, tolerance and cross-tolerance develops between ethanol and benzodiazepines, resulting in reduced potency and efficacy (125). In human alcoholics, Romeo *et al.* (126) have found markedly decreased levels of allopregnanolone during early withdrawal from ethanol. Overall, there is a strong scientific rationale for an important role for neuroactive steroids in the pathophysiology of alcohol withdrawal seizures. Thus, ganaxolone might provide an alternative approach to seizure therapy in patients with alcohol withdrawal symptoms.

Cocaine withdrawal seizures

Ganaxolone has not yet been tested in human subjects with cocaine withdrawal seizures. Nevertheless, it offered protection against seizures induced by cocaine treatment in preclinical assessments (45, 50). Cocaine is known to induce seizures and mortality when administered at high doses (127). This is not sensitive to blockade by several $GABA_A$ receptor positive modulators (128). Using a mouse model, ganaxolone and allopregnanolone were investigated for their ability to suppress both the expression (anticonvulsant effect) and development (antiepileptogenic effect) of cocaine-kindled seizures caused by subchronic cocaine administration (50). Allopregnanolone and ganaxolone had similar efficacy in suppressing the development of kindling. In addition, ganaxolone attenuated cocaine-induced sucrose intake, an effect similar to that caused by the dopamine antagonist haloperidol (129), indicating an extended spectrum of pharmacological interaction between ganaxolone and cocaine. Although the molecular basis of this interaction remains unclear, ganaxolone appears to have a marked protective effect on cocaine withdrawal, and hence might effectively suppress the incidence of seizures in people with cocaine addiction.

Premenstrual syndrome

Premenstrual syndrome (PMS) is a menstruation-related, chronic, cyclical disorder manifested by emotional and physical symptoms in the second half of the menstrual cycle. Premenstrual dysphoric disorder (PMDD) is more severe than PMS, with women reporting severe psychological symptoms of depression, anxiety and mood swings, in addition to the more common complaints of bloating and breast pain. The etiology of PMS is unknown. For years, PMS was attributed to various abnormalities of ovarian hormone secretion during the luteal phase (130, 131), but recent studies report that progesterone-derived neuroactive steroids may be important for the clinical manifestations of PMS (118, 132, 133). Many brain regions (*e.g.*, the amygdala) that contain $GABA_A$ receptors also contain enzymes that reduce the A-ring of progesterone to allopregnanolone (Fig. 1) (14, 134). In normal women, allopregnanolone levels follow a similar time course to progesterone throughout the menstrual cycle, with greater levels in the luteal phase than in the follicular phase (135).

Like other positive allosteric modulators of $GABA_A$ receptors, neuroactive steroids have potent anxiolytic activity in several animal models of anxiety (136-141). Moreover, fluoxetine, a specific serotonin uptake inhibitor (SSRI), dose-dependently increases brain allopregnanolone levels (142), suggesting that elevated neuroactive steroid synthesis could be involved in the anxiolytic and antidysphoric actions of fluoxetine. Moreover, there is a pronounced change in allopregnanolone levels in patients with induced panic attacks (143, 144). These studies suggest that alterations in progesterone-derived allopregnanolone and other neuroactive steroids may predispose certain patients to dysphoria, and hence may facilitate the pathogenesis of PMS. This is supported by the fact that serum concentrations of allopregnanolone during the luteal phase are lower in women with PMS than women without PMS (118, 119, 133, 145, 146), and that withdrawal from progesterone (and thus allopregnanolone) increases anxiety-like behavior in rats (90). Withdrawal from chronic allopregnanolone upregulates hippocampal α4 subunit expression, leading to reduced anxiolytic efficacy of benzodiazepines (91, 147, 148). Because of the cross-tolerance to benzodiazepines that occurs after chronic neuroactive steroids (47), there is a marked loss of sensitivity to benzodiazepines in patients with PMS (120).

Furthermore, the sulfated neuroactive steroids pregnenolone sulfate (PS) and dehydroepiandrosterone sulfate (DHEAS), which block $GABA_A$ receptor function, have been shown to be anxiogenic in mouse anxiety tests (141, 149). These sulfated steroids are present in the brain at relatively high concentrations compared with many other neuroactive steroids (55, 150). It is therefore proposed that PS and DHEAS could be antagonists of allopregnanolone. For example, elevated levels of PS have been observed in women suffering from anxiety disorders (133). When less of the anxiolytic neuroactive steroids such as allopregnanolone are produced, unopposed actions of PS or DHEAS may provoke anxiety-like dysphoria and precipitate PMS. It is therefore speculated that women with PMS might not only be deprived of an anxiolytic neuroactive steroid, but they might also be exposed to higher concentrations of a neuroactive steroid that heightens anxiety.

In view of the possible neurosteroid deficiency in some women with PMS, exogenous ganaxolone, by virtue of its powerful effects on GABAergic transmission, would be expected to have therapeutic utility. Indeed, ganaxolone offers protection against behavioral changes induced by PTZ, which represents a model for anxiety behavior in rodents (151). Moreover, ganaxolone significantly reverses the behavioral disruptions (*e.g.*, locomotor depression) induced by other convulsant/anxiogenic agents such as bicuculline and picrotoxin (152). Ganaxolone also has robust activity in the Geller-Seifter model of punished responding in rats at doses comparable to those effective in the PTZ- and bicuculline-induced

seizure models (K.E. Vanover, J. Belluzzi and R.B. Carter, unpublished results). These anxiolytic effects of ganaxolone are directly comparable to those of diazepam, a benzodiazepine widely used for anxiety disorders. However, benzodiazepines induce or lose their sensitivity following repeated dosing and produce undesirable sedative-cognitive side effects. Moreover, repeated administration of natural (*e.g.*, pregnanolone) or synthetic neuroactive steroids (*e.g.*, Co-2-6749) does not produce tolerance to their antianxiety effects in preclinical models (63, 115, 153). Hence, ganaxolone might provide an alternative therapy for the effective management of PMS.

Conclusions

Ganaxolone is a unique anticonvulsant that belongs to a novel class of synthetic neuroactive steroids (epalons). Neuroactive steroids are positive allosteric modulators of $GABA_A$ receptor function acting via a specific site that is distinct from that of benzodiazepines and barbiturates. Ganaxolone is structurally very similar to the endogenous neurosteroid allopregnanolone, but it does not produce any classical hormonal side effects. Ganaxolone is orally active, and highly effective in GABA-related and kindling seizure models. It is well tolerated and retains protective efficacy upon long-term therapy. Ganaxolone has shown efficacy in clinical studies in adult patients with epilepsy and also in children with refractory infantile spasms. Ganaxolone offers a favorable pharmacokinetic and adverse event profile. Based on the pharmacological studies of ganaxolone in the first clinically relevant animal model of perimenstrual catamenial epilepsy, it is suggested that ganaxolone might provide a rational, nonhormonal drug therapy for women with catamenial seizures, a disorder for which there is currently no specific, FDA-approved therapy. Preclinical studies suggest that ganaxolone may have additional therapeutic utility in the management of PMS and other mood disorders.

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