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REVIEW

PARADOXICAL EFFECTS OF GABA-A MODULATORS MAY EXPLAIN SEX STEROID INDUCED NEGATIVE MOOD SYMPTOMS IN SOME PERSONS

T. BÄCKSTRÖM,[a]* D. HAAGE,[a] M. LÖFGREN,[a] I. M. JOHANSSON,[a] J. STRÖMBERG,[a] S. NYBERG,[a] L. ANDRÉEN,[a] L. OSSEWAARDE,[b] G. A. VAN WINGEN,[b,c] S. TURKMEN[a] AND S. K. BENGTSSON[a]

[a]*Umeå Neurosteroid Research Center, Department of Clinical Sciences, University of Umeå, SE-901 85 Umeå, Sweden*

[b]*Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands*

[c]*Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

Abstract—Some women have negative mood symptoms, caused by progestagens in hormonal contraceptives or sequential hormone therapy or by progesterone in the luteal phase of the menstrual cycle, which may be attributed to metabolites acting on the GABA-A receptor. The GABA system is the major inhibitory system in the adult CNS and most positive modulators of the GABA-A receptor (benzodiazepines, barbiturates, alcohol, GABA steroids), induce inhibitory (e.g. anesthetic, sedative, anticonvulsant, anxiolytic) effects. However, some individuals have adverse effects (seizures, increased pain, anxiety, irritability, aggression) upon exposure. Positive GABA-A receptor modulators induce strong paradoxical effects including negative mood in 3%–8% of those exposed, while up to 25% have moderate symptoms. The effect is biphasic: low concentrations induce an adverse anxiogenic effect while higher concentrations decrease this effect and show inhibitory, calming properties. The prevalence of premenstrual dysphoric disorder (PMDD) is also 3%–8% among women in fertile ages, and up to 25% have more moderate symptoms of premenstrual syndrome (PMS). Patients with PMDD have severe luteal phase-related symptoms and show changes in GABA-A receptor sensitivity and GABA concentrations. Findings suggest that negative mood symptoms in women with PMDD are caused by the paradoxical effect of allopregnanolone mediated via the GABA-A receptor, which may be explained by one or more of three hypotheses regarding the paradoxical effect of GABA steroids on behavior: (1) under certain conditions, such as puberty, the relative fraction of certain GABA-A receptor subtypes may be altered, and at those subtypes the GABA steroids may act as negative modulators in contrast to their usual role as positive modulators; (2) in certain brain areas of vulnerable women the transmembrane Cl^- gradient may be altered by factors such as estrogens that favor excitability; (3) inhibition of inhibitory neurons may promote disinhibition, and hence excitability.

*Corresponding author. Tel: +46-907852144.
E-mail address: torbjorn.backstrom@obgyn.umu.se (T. Bäckström).
Abbreviations: fMRI, functional magnetic resonance imaging; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome.

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Key words: premenstrual syndrome, GABA-A receptor, paradoxical, GABA-steroid, neurosteroid.

Contents

GABA-A receptor agonists are known to induce sedation, calmness, and anxiolytic and antiepileptic effects. However, in several clinical situations the effect of GABA-A receptor-positive modulators is opposite to that expected. This is called a paradoxical reaction or a paradoxical effect.

For example, some patients react to benzodiazepines with irritability, aggression, confusion, violent behavior, and loss of impulse control (Ben-Porath and Taylor, 2002; Hall and Zisook, 1981; Honan, 1994). Reports indicate that all GABA-A receptor agonists induce strong negative symptoms such as anxiety, irritability, or aggression in 3%–6% of human subjects, while moderate symptoms are induced in 20%–30% (Masia et al., 2000; Weinbroum et al., 2001). Interestingly, the prevalence of premenstrual dysphoric disorder (PMDD; American Psychiatric Association [APA], 1994) among women of reproductive age is in a similar range, 3%–8%, while 25%–35% have milder symptoms of premenstrual syndrome (PMS; American College of Obstetricians and Gynecologists [ACOG], 2000; Sveindottir and Bäckström, 2000). Weinbroum et al. reported a 10.2% incidence of paradoxical effects of midazolam in patients who underwent surgery. They also showed that treatment with a benzodiazepine receptor antagonist effectively reversed the paradoxical behaviors (Weinbroum et al., 2001). The paradoxical effect can also be induced by barbiturates, for example, during evaluation of epileptic

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patients for epilepsy surgery (Kurthen et al., 1991; Lee et al., 1988). Alcohol is also active on the GABA-A receptor and has been associated with paradoxical effects such as increased irritability and aggression. A number of human studies have reported increased aggression after alcohol consumption (Cherek et al., 1992; Dougherty et al., 1996). The symptoms induced by the paradoxical effect of these GABA-A receptor-active drugs are depression, irritability, aggression, and other symptoms also known to occur during the luteal phase in women with PMDD (APA, 1994) or PMS (ACOG, 2000) or during the progestagen treatment phases of postmenopausal hormone replacement treatment (Björn et al., 2002; Andréen et al., 2005).

Animal studies also show benzodiazepine-heightened aggression that is similar to the paradoxical increases in aggressive outbursts observed in humans (Ferrari et al., 1997; Gourley et al., 2005; Miczek, 1974). The use of benzodiazepine antagonists seems to counteract the benzodiazepine-heightened aggression in laboratory animals as in humans (Gourley et al., 2005; Weerts et al., 1993). Many reports from animal studies show that alcohol is consistently associated with increased aggressive and violent behavior (Miczek, 1974; de Almeida et al., 2004; Fish et al., 2001; Miczek et al., 1997). Studies have shown that pretreatment with flumazenil (a benzodiazepine antagonist) or β-CCt (a subunit specific GABA-A receptor antagonists) prevents alcohol-heightened aggressive behavior (de Almeida et al., 2004; Weerts et al., 1993). As allopregnanolone and other GABA-steroids are positive GABA-A receptor modulators, similar to benzodiazepines and barbiturates, it is reasonable to propose that allopregnanolone may also induce paradoxical effects in sensitive individuals. Such paradoxical effects have been induced by allopregnanolone in animal experiments (Beauchamp et al., 2000; Miczek et al., 2003).

The paradoxical effect induced by positive GABA-A receptor modulators shows an inverted U-shaped relationship between concentration or dosage and effect. In rodents an inverted U-shaped relation has been noted between benzodiazepine, alcohol, or allopregnanolone dosage/levels and irritability/aggression (Miczek et al., 2003). In humans similar relationships exist. In postmenopausal women receiving progesterone a biphasic relation has been shown between negative mood symptoms and allopregnanolone concentrations in blood (Andréen et al., 2006). Negative mood increases with increasing serum concentration of allopregnanolone up to the maximum concentration seen during the luteal phase of the menstrual cycle, but with further increase in allopregnanolone concentration there is a decrease in symptom severity (Andréen et al., 2005, 2006). A biphasic effect can also be seen when different dosages of medroxyprogesterone (MPA) or natural progesterone are given to postmenopausal women taking hormone therapy (HT). These women feel worse on a lower dosage of MPA or progesterone than on a higher dosage or placebo (Andréen et al., 2005, 2006; Björn et al., 2002), and those who had PMS are over-represented among patients who react negatively to progestagens (Björn et al., 2000). MPA has also been shown in animals to increase allopregnanolone concentrations in several brain areas (Bernardi et al., 2006).

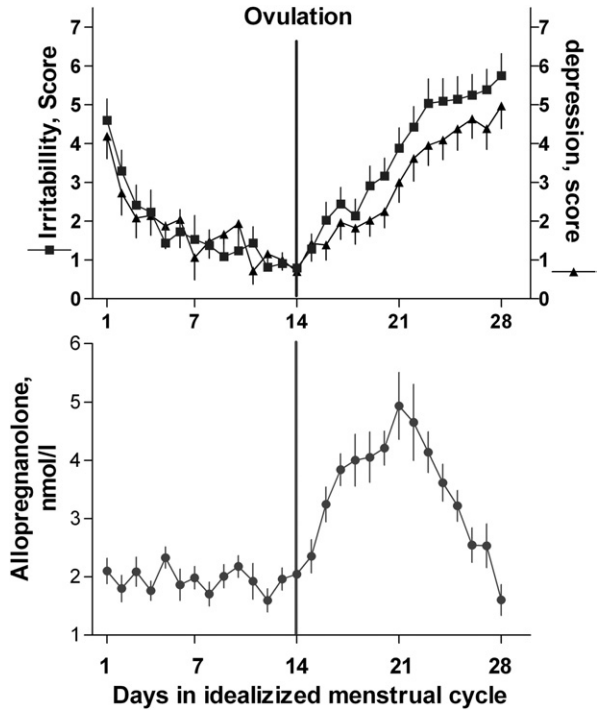

Fig. 1. Daily ratings of irritability and depression during the menstrual cycle in women with PMDD/severe PMS (two cycles/patient, $n=12$). Blood samples for hormone and allopregnanolone assays were taken regularly. Data are centered on the day of onset of menstruation and the day of ovulation. Allopregnanolone concentration increase is related to symptom increase during menstrual cycle in women with severePMS. From Bäckström et al., CNS Drugs 2003;17:325–342, with permission from Adis Wolters Kluwer Health.

PREMENSTRUAL DYSPHORIC DISORDER (PMDD) AND PREMENSTRUAL SYNDROME (PMS)

In women with PMDD or PMS the relation between sex steroids, GABA steroids, and mood symptoms during the menstrual cycle is very obvious (Fig. 1, Bäckström et al., 1983). The sex hormones estradiol and progesterone show regular predictable changes during the menstrual cycle. In parallel with progesterone, the neuroactive steroids and positive GABA-A receptor modulators allopregnanolone, tetrahydrodeoxicorticosterone (THDOC), and pregnanolone increase in serum (Wang et al., 1996; Sundström et al., 1998; Tuveri et al., 2008). Allopregnanolone can be synthesized in the central nervous system but the major contributor to the concentration in the brain during the luteal phase of the menstrual cycle is the corpus luteum of the ovary (Bixo et al., 1997; Ottander et al., 2005). In fertile women plasma levels of allopregnanolone are approximately 0.2–0.5 nmol/L in the follicular phase and up to 4 nmol/L in the luteal phase. In the third trimester of

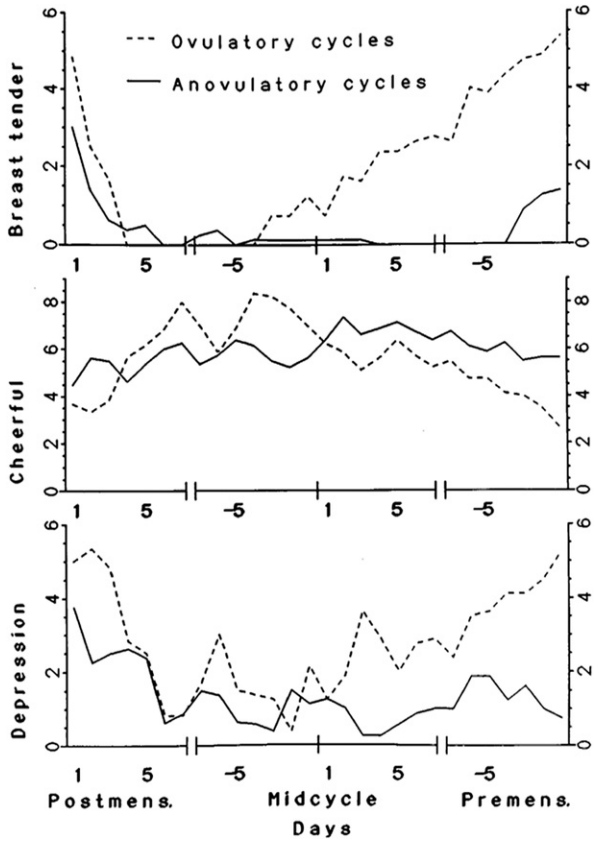

Fig. 2. Daily ratings of depression in the same patients (n=8) during two menstrual cycles showing one ovulatory cycle with typical cyclic mood changes and one anovulatory cycle. Symptom data are centered on day of onset of menstruation and day of ovulation. Symptom cyclicity disappears in the anovulatory cycle. Ovulation is diagnosed with serum estradiol and progesterone assays. From Hammarbäck et al., Acta Endocrinol 1991;125:132–137, with permission from BioScientifica.

a pregnancy these levels increase to more than 100 nmol/L (Bicikova et al., 1995; Luisi et al., 2000).

PMDD is defined by the recurrence of mental and physical symptoms during the luteal phase of the ovulatory cycles of fertile women. Severe irritability, depression, and mood lability distinguish PMDD. The rise in progesterone and allopregnanolone concentrations seen in the luteal phase is required for the development of PMDD symptoms. In anovulatory cycles, either spontaneous or induced by gonadotropin-releasing hormone (GnRH) agonists, the cyclicity in symptoms disappears (Muse et al., 1984; Hammarbäck and Bäckström, 1988; Hammarbäck et al., 1991; Fig. 2). During hormone treatment in postmenopausal women the sequential addition of oral progesterone, which is highly convertable to allopregnanolone (Andréen et al., 2006), is associated with the development of negative mood symptoms (Fig. 3). The symptoms induced by progesterone are similar to symptoms seen in PMDD, including depression, anxiety, and irritability (Andréen et al., 2003; Björn et al., 2000; Hammarbäck et al., 1985; Magos et al., 1986). However, the classical endocrine progesterone receptor is not involved in the pathophysiologies of PMS or PMDD, as the progesterone receptor antagonist, mifepristone (RU 486), fails to reduce the physical or behavioral symptoms of PMS or PMDD (Chan et al., 1994; Schmidt et al., 1991). Therefore, metabolites of progesterone, such as allopregnanolone that act on the GABA-A receptor in the CNS, are of increasing interest (Majewska et al., 1986).

GABA-A RECEPTOR SENSITIVITY IN PMDD AND PMS

Allopregnanolone concentrations rise during the luteal phase in all women, but why do not all women have PMDD or PMS? Several studies show that women with PMDD or PMS have a changed sensitivity to GABA-A receptor-active positive modulators (benzodiazepins, alcohol, and pregnanolone) than do controls (Sundström et al., 1997, 1998; Nyberg et al., 2004). It has been demonstrated that the severity of premenstrual symptoms in women with PMDD is related to their sensitivity to benzodiazepines and GABA steroids (Sundström et al., 1998), while that sensitivity is normalized during treatment with serotonin-reuptake inhibitors (Sundström and Bäckström, 1998). In addition prepulse inhibition of the startle response indicates that a CNS-related change in sensitivity, rather than a difference in the allopregnanolone levels, characterizes the difference between women with PMDD and controls (Kask et al., 2008). The GABA levels in patients with PMDD are also different from those in controls (Epperson et al., 2007). It has also been shown that women with PMDD respond differently from controls to ovarian hormones in anovulatory cycles induced by GnRH-agonists, with negative mood symptoms indicating that they have increased sensitivity to progesterone and estradiol (Schmidt et al., 1998; Segebladh et al., 2009).

Functional magnetic resonance imaging (fMRI) can investigate the activity in defined brain areas during emo-

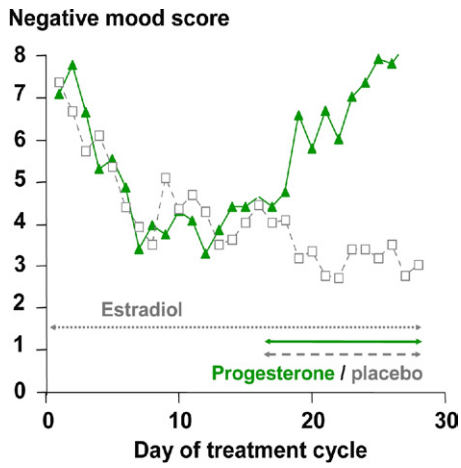

Fig. 3. Mood changes in postmenopausal women taking sequential hormone replacement therapy in a cross-over double blind controled study. Progesterone but not placebo is accompanied with negative mood symptoms in postmenopausal women when receiving estrogen+progesterone compared to placebo. From Andreén et al., Psychoneuroendocrinology 2005;30:212–224, with permission from Elsevier.

tional stimulation and under drug treatment. In control women, fMRI shows significant changes in responses in the brain in relation to the hormone variations during the menstrual cycle (Fernández et al., 2003). Studies using brain imaging techniques show that women with PMDD or PMS react differently from controls to stressful stimuli (Protopopescu et al., 2008; Rapkin et al., 2011). Premenstrual changes in reward-related neural activity have also been shown. Reward anticipation assessed by fMRI in the ventral striatum showed increased responses in the premenstrual compared to postmenstrual phase. The follicular-premenstrual difference was also related to the severity of premenstrual symptoms. Increases in reward-cue responsiveness have been associated with dopamine (DA) withdrawal states (Ossewaarde et al., in press). Allopregnanolone is known to influence the DA action but with different effects depending on hormonal status and brain area (Löfström and Bäckström, 1978, 1981; Laconi et al., 2007). Women with PMDD or PMS show increased stress-sensitivity during the late luteal phase (Brown and Lewis, 1993; Facchinetti et al., 1992; Harrison et al., 1989).

Functional MRI studies in women show opposite responses to stress induction during different phases of the menstrual cycle, with an unexpected lower response in the late luteal phase. In addition, a larger increase in the allopregnanolone concentration from the follicular to the luteal phase was related to smaller amygdala and medial prefrontal cortex responses after stress induction in the late luteal phase (Ossewaarde et al., 2010). This effect appears to be mediated by changes in neural excitability associated with fluctuations of allopregnanolone across the menstrual cycle (Ossewaarde et al., 2010). GABA concentrations have been studied in PMDD patients and controls using MRI studies of the occipital cortex and they indicate that the GABAergic system is substantially modulated during the menstrual cycle. PMDD patients show higher brain GABA concentration during the follicular phase than do controls, suggesting that PMDD patients have a dysfunction in the GABA system (Epperson et al., 2002).

The amygdala is related to emotional experience, therefore the amygdala response to emotional stimulation when oral progesterone is given is of interest. Administration of progesterone such that a moderate allopregnanolone plasma concentration is reached increases the neural response to angry and fearful faces selectively in the amygdala (van Wingen et al., 2008). This is opposite to the benzodiazepine response, which at a dosage giving an anxiolytic effect is a decrease in the amygdala fMRI response to angry and fearful face stimuli (Paulus et al., 2005). However, higher allopregnanolone concentrations are associated with a decrease in amygdala reactivity, indicating a biphasic effect of allopregnanolone (van Wingen et al., 2007). These results show a neural mechanism by which progesterone/allopregnanolone could induce anxiety and negative mood. As the effects of progesterone likely are mediated by allopregnanolone, this paradoxical increase in amygdala activity might reflect a disinhibition of the principal neurons in the amygdala. The increased amygdala response was observed in the fMRI studies when the allopregnanolone level was similar to those found in the luteal phase, or during early pregnancy (Wang et al., 1996; Parizek et al., 2005), whereas higher concentrations gave a different response. In rodents high doses of allopregnanolone injected into the amygdala gives anxiolysis (Akwa et al., 1999).

In sensitive women physiological luteal phase levels of allopregnanolone seem to provoke a different response from higher pharmacological levels or dosages. Higher levels or dosages produce sedation, antiepileptic, and anxiolytic effects (Bäckström et al., 2003). Most women notice no effect from allopregnanolone in the physiological range, but for those who are sensitive to allopregnanolone, it seems to evoke a paradoxical response with negative mood symptoms, excitation, and irritability. Women with PMDD or PMS have been shown to react differently from controls to GABA-A receptor active compounds. Different alterations or abnormalities in brain function could serve as plausible explanations for why some women experience an averse response to allopregnanolone. These possible explanations may provide a focus for additional studies in both animals and humans.

POSSIBLE EXPLANATIONS FOR THE PARADOXICAL EFFECT OF GABA-STEROIDS

One hypothesis for the paradoxical effects of GABA-steroids is based on the finding that GABA-evoked currents at GABA-A-receptors with the alpha4,beta2,delta subunit combination can be inhibited by allopregnanolone (Shen et al., 2007). During stress allopregnanolone and other GABA-steroids are produced, and under nonstressed circumstances allopregnanolone gives an anxiolytic and calming effect (Bitran et al., 1999). However, Smith and colleagues showed that during puberty female mice reacted with increased anxiety to stress (Shen et al., 2007). In humans, puberty is often a period characterized by mood swings and anxiety. Smith and her group also used electrophysiological recordings in mice CA1 hippocampal pyramidal cells to show that allopregnanolone changed from being a positive modulator of the GABA-A-receptor at the time before and after puberty to being a negative modulator at the time of puberty. They also showed that the change in effect was related to expression of the alpha4,beta2,delta subunit combination (Shen et al., 2007). The GABA-A-receptor subunit combinations that contain the delta subunit are known to be very sensitive to GABA-steroids and are activated by lower concentrations of allopregnanolone than other receptor subtypes (Wohlfarth et al., 2002; Liang et al., 2004). Therefore, the action of allopregnanolone at the alpha4,beta2,delta containing GABA-A receptors provides a mechanism for the generation of negative mood at puberty. Whether this mechanism underlies the symptoms of PMDD or PMS is still to be evaluated. However, the alpha4,beta,delta subunit composition is also a key factor in the progesterone withdrawal model for PMDD (Gallo and Smith, 1993; Smith et al., 1998a), and these results are consistent with those

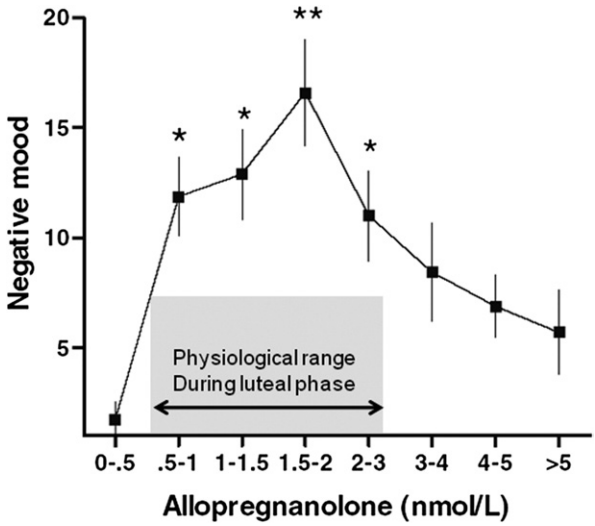

Fig. 4. Negative mood ratings from the same day as blood samples were taken. Symptoms increase related to increasing plasma allopregnanolone in postmenopausal women taking oral progesterone. The shaded area indicates the normal allopregnanolone range during the luteal phase of the menstrual cycle. * indicates significantly higher than 0–.5 value of mood $P<0.05$; ** $P<0.01$. From Andréen et al., Psychopharmacology (Berl) 2006;187:209–221, with permission from Springer.

from PMDD patients who had a decreased sensitivity to benzodiazepines (Sundström et al., 1998). The alpha4 subunit is also related to the development of acute tolerance to allopregnanolone in an anesthesia model (Birzniece et al., 2006).

THE ALTERED Cl^- GRADIENT HYPOTHESIS

We would like to take the opportunity to suggest another hypothesis, based mainly on a theoretical line of reasoning, but of interest because a number of findings give support to the concept. The basic idea is that the reversal potential for Cl^- over the cell membrane may be shifted, especially in vulnerable individuals, and in certain brain regions (Fig. 5). In adult vertebrates the intracellular Cl^- concentration of neurons is relatively low and activation of GABA-A receptors gives an inhibition of neuronal activity. In contrast, during fetal development the intracellular Cl^- concentration is comparably high, and because of that activation of GABA-A-receptors causes excitation (Kahle et al., 2008). However, elevated intracellular Cl^- concentrations can also produce GABA-evoked excitability in the adult brain, both postsynaptic (Khirug et al., 2008; Szabadics et al., 2006; Martina et al., 2001; Gulácsi et al., 2003; Moenter and DeFazio, 2005) and in presynaptic terminals (Haage et al., 2002).

The intracellular Cl^- concentration is determined by the activity of inward and outward directed transmembrane Cl^- pumps, where the major inward pump is NKCC1 and the major outward pump is KCC2 (De Koninck, 2007; Price et al., 2005, 2009). In adult animals and probably also in humans, the outward directed pump KCC2 dominates, keeping the intracellular Cl^- concentration low. However in neuropathic pain, for example, the Cl^- pump KCC2 is less efficient, due to neuronal damage, and is inhibited by growth factors such as brain-derived neurotrophic factor (BDNF; Price et al., 2005). That the activity of the chloride pumps can change in adulthood is also shown in human brain tissue close to epileptic foci in patients (Huberfeld et al., 2007; Muñoz et al., 2007). Interestingly, estradiol is one factor that increases the activity of NKCC1 under normal physiological conditions and thus increases the intracellular Cl^- concentration (Nakamura et al., 2004; Galanopoulou, 2008). Estradiol dose dependently increases the mood-provoking effect of progestagens in women (Björn et al., 2003), and worsens the negative mood in women with PMDD/PMS (Dhar and Murphy, 1990).

Assuming that the Cl^- gradient is shifted, would a GABA-A-receptor activation then necessarily lead to excitation or would it just shunt the action potentials, meaning that the Cl^- gradient is so dominant that further depolarization and activation of voltage-sensitive sodium channels is not possible? Furthermore, if that is the case, would a further GABA-A-receptor activation lead to inhibition? The answers to these questions are rather complex, but the report of Prescott and coworkers actually shows that increased excitability is possible, at least in theory. They suggest that at a more positive equilibrium potential of Cl^- a moderate increase in GABAergic activity gives increased excitation, whereas a larger GABAergic activity gives the

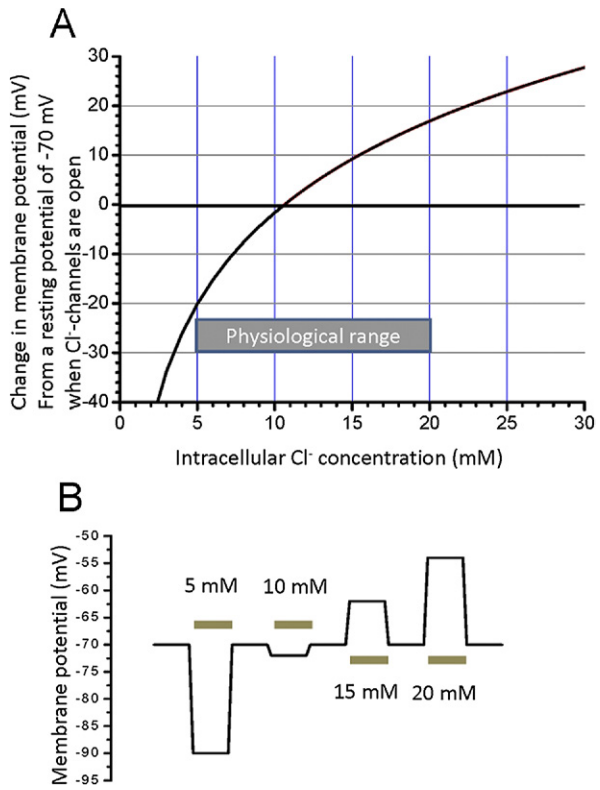

Fig. 5. Change in membrane potential due to activation (opening) of GABA-A receptors. (A) Shows the change in membrane potential from the resting potential of −70 mV. (B) Shows the change in membrane potential due to GABA-A receptor activation at different intracellular Cl^- concentrations of 5, 10, 15, and 20 mM.

opposite effect (Prescott et al., 2006), thus providing a plausible explanation for the bell-shaped dose–response curve in Fig. 4. Therefore, an altered activity of KCC2 or NKCC1 in adulthood may serve as a hypothesis for the paradoxical effect of GABA-A-receptor modulators.

A third possible mechanism underlying the GABA-paradox is disinhibition of inhibitory neurons. The specific combination of subunits determines the receptor sensitivity to different GABA-A receptor modulators and influences the function of the receptor (Belelli et al., 2002; Strömberg et al., 2006). The extra-synaptic delta containing GABA-A receptors are of special interest, as they seem to be more sensitive to GABA-steroids than other types of subunit combinations (Mody, 2008). It is possible that one type of inhibitory neuron contains GABA-A receptors with delta subunits, while the next inhibitory neuron in order contains another subunit combination, making it less sensitive to GABA-steroids. It has also been reported that the receptor subunit composition and sensitivity to GABA modulators can be modulated by environmental factors such as stress (Biggio et al., 1990; Concas et al., 1996) and hormonal therapy (Smith et al., 1998b). In humans the paradoxical increase in the activity of the amygdala shown in the fMRI studies might reflect a disinhibition of the principal neurons of the amygdala via inhibition of inhibitory interneurons. However, higher progesterone or allopregnanolone concentrations are associated with a decrease in amygdala reactivity (van Wingen et al., 2007, 2008). These fMRI results support the observation that allopregnanolone seems to induce negative mood changes in a nonlinear inverted U-shaped curve (Fig. 4).

CHRONIC STRESS AS INDUCER OF PARADOXICAL EFFECTS OF ALLOPREGNANOLONE

Chronic GABA-A receptor activation is a factor that alters GABA-A receptor subunit composition in several parts of the CNS (Barnes, 1996). GABA-A receptor dysfunction has been implicated in chronic stress (Drugan et al., 1989), and certain stress-related affective disorders are especially associated with changes in the amygdala's excitability, implicating a possible dysfunction of the GABAergic system (McEwen, 2002; Braga et al., 2004). Social isolation stress in rodents induces an increase of alpha4 subunit-containing GABA-A receptors in certain areas (Pinna et al., 2006). The expression of the alpha4 subunit is usually low in the brain, except in the thalamus and the dentate gyrus, but enhanced expression of this GABA-A receptor subtype is observed in animal models of premenstrual syndrome (Smith et al., 1998a), epilepsy (Banerjee et al., 1998), alcohol withdrawal (Cagetti et al., 2003), and tolerance (Birzniece et al., 2006). Socially isolated mice are resistant to the sedative effect of diazepam and this resistance seems to be attributable to the decrease of the alpha1 subunit and increase in delta-containing GABA-A receptors. Paradoxically, diazepam acts at other GABA-A receptor subtypes, and increases the locomotor activity of socially isolated mice (Pinna et al., 2006). In socially isolated mice benzodiazepines that are full positive allosteric modulators of the GABA action at GABA-A receptors (e.g. midazolam and triazolam) may, in low doses, increase aggression, thus mimicking the "paradoxical'' increase in aggressive outbursts in a resident-intruder test (Gourley et al., 2005). As mentioned above similar behavior is sporadically observed in human subjects receiving benzodiazepines (Woods et al., 1992; Ben-Porath and Taylor, 2002). In group-living rats a low rank and subordination is clearly stressful, produces a variety of negative effects for the animal, and is regarded as a chronic stress model (Blanchard et al., 1993; Koolhaas et al., 1997; Meerlo et al., 1996; Rygula et al., 2005). The effect of progesterone or allopregnanolone withdrawal is different in submissive rats than in dominant rats in group living (Löfgren, 2009). During an intruder test, increased defensive burying after progesterone withdrawal was seen exclusively in animals exposed to chronic subordination stress (Löfgren, 2009). Increased defensive burying is a common response to a threat during withdrawal from progesterone, allopregnanolone, or alcohol (Gallo and Smith, 1993; Sandbak et al., 1998).

CONCLUSION

There are several mechanisms that can explain paradoxical effects in sensitive persons. The effects seem not to be exclusively related to GABA-steroids. The prevalence for paradoxical effects of GABA-A receptor modulators in the general population is similar to the prevalence of PMDD or PMS. Chronic stress may be one factor that can induce an increased sensitivity to the paradoxical effects of GABA-A receptor positive modulators. Low concentrations or dosages seem to be more provocative than high levels. There are indications that the delta and alpha4 GABA-A receptor subunits are involved in at least the paradoxical GABA-steroid effect. Interesting future studies may investigate the function and polymorphism of the Cl^- pumps in relation to PMDD and PMS and people's different reactions and paradoxical effects from positive GABA-A receptor modulators.

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