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Progesterone receptor antagonist CDB-4124 increases depression-like behavior in mice without affecting locomotor ability

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Summary Progesterone withdrawal has been proposed as an underlying factor in premenstrual syndrome and postpartum depression. Progesterone withdrawal induces forced swim test (FST) immobility in mice, a depression-like behavior, but the contribution of specific receptors to this effect is unclear. The role of progesterone's $GABA_A$ receptor-modulating metabolite allopregnanolone in depression- and anxiety-related behaviors has been extensively documented, but little attention has been paid to the role of progesterone receptors. We administered the classic progesterone receptor antagonist mifepristone (RU-38486) and the specific progesterone receptor antagonist CDB-4124 to mice that had been primed with progesterone for five days, and found that both compounds induced FST immobility reliably, robustly, and in a dose-dependent fashion. Although CDB-4124 increased FST immobility, it did not suppress initial activity in a locomotor test. These findings suggest that decreased progesterone receptor activity contributes to depression-like behavior in mice, consistent with the hypothesis that progesterone withdrawal may contribute to the symptoms of premenstrual syndrome or postpartum depression.
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1. Introduction

Depressive disorders are more common in females than males, indicating that sex steroids may contribute to sex differences in depression (Hyde et al., 2008; Kessler, 2003; Noble, 2005; Steiner et al., 2003), and to reproductive-related depressive syndromes such as postpartum depression or perimenstrual affective disorders (premenstrual syndrome or premenstrual dysphoric disorder) (Payne et al., 2009). The timing of these syndromes coincides with particular hormone fluctuations, which has led some to hypothesize that reproductive-related depression may be a sort of hormone withdrawal syndrome (Kammerer et al., 2006; Meaden et al., 2005; Pearlstein et al., 2005; see also, Gehlert et al., 1999; Gonda et al., 2008). The delay between peak luteal progesterone concentrations and peak symptom severity suggests that progesterone withdrawal may be a contributing factor in

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perimenstrual affective disorders (e.g., Halbreich et al., 1986; Redei and Freeman, 1995) or postpartum depression (MacDonald et al., 1991).

Several methods have been developed to model hormone withdrawal in laboratory animals. There is no standardized nomenclature for the different methods, but we propose general terms to distinguish some of the methods used (see Table 1). Passive, metabolic, surgical, and estrous-cycle dependent methods are the most common approaches for hormone withdrawal, and have consistently been associated with increased depression- or anxiety-like behaviors in laboratory animals (Bekku et al., 2006; Bitran and Smith, 2005; de Chaves et al., 2009; Devall et al., 2009; Gallo and Smith, 1993; Löfgren et al., 2009; Navarre et al., 2010; Schneider and Popik, 2007; Stoffel and Craft, 2004). However, the temporal correlation between steroid withdrawal and depression symptoms in humans or rodents does not in itself identify which receptor systems are involved, since many steroids have multiple receptor targets. The current paper utilizes steroid-receptor antagonists to selectively attenuate progesterone receptor activity to address the specific role of progesterone receptors in the effects of progesterone withdrawal on depression-like and locomotor behavior. We describe this approach as "precipitated withdrawal" to be consistent with other instances where a withdrawal syndrome is induced by blocking a signal at the receptor level rather than removing the signaling molecule from systemic circulation (e.g., precipitated cannabis withdrawal, Budney and Hughes, 2006; precipitated opioid withdrawal, Sadée et al., 2005).

As discussed above, hormone withdrawal treatments in laboratory animals are commonly reported to result in increases in depression-like or anxiety-like behaviors. One standard measure is the forced swim test (FST), in which immobility behavior is thought to indicate a depression-like state. We recently reported that passive progesterone withdrawal increases FST immobility (Beckley and Finn, 2007). However, changes in progesterone concentrations also affect the concentrations of metabolite steroids such as allopregnanolone (ALLO), a positive allosteric modulator of γ-aminobutyric acid type-A receptors ($GABA_A$ receptors). ALLO binds with high affinity to $GABA_A$ receptors where it increases the open-time of the chloride channel (Belelli and Lambert, 2005). Our passive progesterone withdrawal procedure results in decreased plasma progesterone (Beckley and Finn, 2007), but since progesterone is a precursor for ALLO, passive progesterone withdrawal also dramatically reduces brain concentrations of ALLO (Beckley and Finn, unpublished data).

Table 1 Methods of inducing hormone withdrawal in laboratory animals.

Withdrawal type	Method
Passive	Administer hormones for a period of time, then discontinue administration and allow hormones to withdraw as a result of endogenous clearance mechanisms
Metabolic	Administer precursor hormones for a period of time, then co-administer drugs to inhibit metabolism of the precursor, thus withdrawing hormone of interest by blocking its production
Surgical	Allow the animal to produce its own hormones (often after inducing pseudopregnancy), then surgically remove the steroidogenic glands
Estrous cycle dependent	Allow the animal to produce and withdraw from its own hormones according to its estrous cycle
Precipitated	Administer hormones for a period of time, then co-administer drugs that antagonize the target receptors of interest

The metabolic relationship between concentrations of ALLO and progesterone led some to hypothesize that ALLO withdrawal might underlie FST immobility during progesterone withdrawal. Administering the 5α-reductase inhibitor finasteride to block the conversion of progesterone to ALLO (a method of metabolic ALLO withdrawal) resulted in increased FST immobility to a level consistent with the immobility observed during passive progesterone withdrawal (Beckley and Finn, 2007). Related evidence has led many in the field to suggest a role for ALLO in depressive-like behavior in laboratory rodents (e.g., Dong et al., 2001; Molina-Hernández et al., 2005). Furthermore, two studies have shown that progesterone receptors are not required for progesterone to have anxiolytic effects on rodent behavior (Frye et al., 2006; Reddy et al., 2005). Thus, much of the existing research that has examined relationships between progesterone and depression has focused on progesterone as a precursor for ALLO. While previous studies have convincingly demonstrated that intracellular progesterone receptors are not necessary for certain behavioral effects of progesterone, those studies have not rigorously ruled out a possible role for progesterone receptors in affective behaviors.

The present set of experiments tested whether the non-selective progesterone receptor antagonist mifepristone (RU-38486) and the selective progesterone receptor antagonist CDB-4124 would increase FST immobility when administered in a precipitated withdrawal procedure. Mifepristone is a high-potency, high-affinity ligand for the progesterone receptor, but it is neither purely antagonistic at progesterone receptors, nor is it selective for progesterone receptors. In some cases mifepristone has progesterone-enhancing or progesterone-agonist effects (Chien et al., 2009; Taylor et al., 1998), and it is a potent anti-glucocorticoid (Attardi et al., 2004). CDB-4124 has decreased binding affinity and decreased anti-progesterone potency compared to mifepristone, based on its ability to inhibit the effects of the synthetic progestin R5020 (promegestone) (Attardi et al., 2004). Nonetheless, CDB-4124 is still a very potent progesterone receptor antagonist (Benagiano et al., 2008a), and compared to mifepristone has greatly reduced binding affinity for glucocorticoid receptors as well as decreased *in vivo* anti-glucocorticoid effects (Attardi et al., 2004). We also tested the effects of CDB-4124 or finasteride on locomotor activity to determine whether FST immobility was related to a general suppression of activity. Together, the results of these findings provide new information about the potential involvement of progesterone receptors in depression-like behavior of mice.

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