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Finasteride inhibits the progesterone-induced spike-wave discharges in a genetic model of absence epilepsy

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Abstract

Previously, it was found that progesterone aggravates spike-wave discharges (SWD) in WAG/Rij rats in a nongenomic way. In order to elucidate whether the regulatory effect of progesterone depends on its conversion to allopregnanolone, the effect of finasteride, a 5α-reductase inhibitor, on progesterone-induced increase in SWD was studied in the same model for absence epilepsy. Progesterone (10 and 20 mg/kg ip) dose-dependently increased the number of SWD (by 54% and 97%, respectively) during the first hour postinjection. Pretreatment of rats with finasteride (50 mg/kg sc) blocked the progesterone-induced enhancement of SWD. Finasteride alone had no effect on the number of SWD, up to 24 h following its administration. It is concluded that finasteride blocked the progesterone-induced increase in SWD, which indicates that this action of progesterone is mediated by its neuroactive metabolite allopregnanolone.

Keywords: Progesterone; Finasteride; 5α-reductase; WAG/Rij rats; Spike-wave discharges; Generalized absence epilepsy

1. Introduction

In addition to its endocrine role, progesterone has been found to act as neuromodulator within the CNS (Kawata, 1995; Fink, 1994). Progesterone attenuates neuronal excitability, has anticonvulsant actions in various animal models of convulsive epilepsy and retards development of kindling (Holmes and Weber, 1994; Kokate et al., 1999; Landgren et al., 1987; Mohammad et al., 1998; Woolley and Timiras, 1962). Furthermore, blood concentrations of progesterone are significantly lower in catamenial epilepsy patients compared to nonepileptic controls (Mattson and Cramer, 1985). In contrast to convulsive epilepsy, progesterone seems to aggravate absence seizures. Scarce clinical data show that in women with absence epilepsy the seizure frequency is positively correlated with blood progesterone concentration (Bäckström et al., 1990) and that administration of this hormone exacerbates absence seizures (Grunewald et al., 1992).

It has been proposed that a particular strain of rats, WAG/Rij, is a useful genetic model for generalized absence epilepsy in man (Van Luijtelaar and Coenen, 1986; Coenen et al., 1992). All rats of this strain older than 6 months show 7–10 Hz spike-wave discharges (SWD) in the cortical EEG, together with concomitant behavioural episodes of twitching of the vibrissae and accelerated breathing. This model has been amply validated by pharmacological and behavioural studies as a genetic model of childhood absence epilepsy (Peeters et al., 1988; Coenen et al., 1991, 1992; Drinkenburg et al., 1991; Van Luijtelaar et al., 1991a,b). This and other genetic models differ however, from human absence epilepsy in developmental aspects, since absence epilepsy is a childhood disease, which may disappear or transforms into more serious type of epilepsy, while in rats SWD appear after puberty and do not diminish throughout life. Neurochemical basis for the abovementioned age-related differences in pathogenesis of absences in man and rats are yet to be elucidated.

The classical effects of progesterone are exerted on gene transcription through the activation of intracellular receptors, which are widely distributed in the central nervous system. However, its genomic effects do not seem to play an important role in seizure regulation (Budziszewska et al., 1999) since the antagonist of the intracellular receptor, RU-38486, was not able to antagonize the effects of progesterone. Beside genomic action, progesterone has been shown

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to affect neuronal activity via its metabolite—3α,5α-tetrahydroprogesterone (allopregnanolone), a positive modulator of the $GABA_A$ receptor (Majewska et al., 1986). Kokate et al. (1999) established that the inhibition of pentylenetetrazol-induced seizures by progesterone are in fact exerted by allopregnanolone. Moreover, Frye and Scalise (2000) showed that inhibition of 5α-reductase blocked the anti-seizure effects of progesterone in the perforant pathway stimulation model. In contrast, in chemical models of absence epilepsy i.e., evoked by low dose of pentylenetetrazol or gamma-hydroxybutyric acid a synthetic derivative of allopregnanolone–ganaxolone exacerbated seizures in rats (Snead, 1998).

Taken into account the lack of effect of an antagonist of intracellular progesterone receptor-RU 38486 on progesterone-induced increase of SWD in WAG/Rij rats, it has been hypothesised, that the effect of this hormone on SWD is exerted by its metabolite, allopregnanolone (Budziszewska et al., 1999; Van Luijtelaar et al., 2001). In order to test this hypothesis, the effect of finasteride, an inhibitor of 5α-reductase, on the progesterone action on SWD in WAG/Rij male rats was investigated. Finasteride blocks the conversion of progesterone to 5α-dihydroprogesterone, which is next reduced by 3α-hydroxysteroid oxidoreductase to allopregnanolone. It has been shown, that 5α-reductase is a rate-limiting enzyme in the synthesis of allopregnanolone (Stoffel-Wagner, 2001; Russell and Wilson, 1994). In order to investigate whether the blockade of the conversion of endogenous progesterone to allopregnanolone can affect SWD, the influence of finasteride alone on 24-h EEG was also measured. Furthermore, since progesterone may affect animal's behavior, which in turn can influence the number of SWD, behavioural observations were also carried out during the EEG recording.

2. Materials and methods

Male WAG/Rij rats, born and raised in our laboratory, were used. Rats lived in groups of two or three under standard laboratory conditions with ad libitum food and water on a reversed 12:12 light–dark cycle. Bright light (300–400 Lx) was on from 19:00 to 7:00 h, otherwise dimmed red lights (2–3 Lx). Rats were between 9 and 10 months old at the time of surgery and varied in body weight from 300 to 360 g. The experimental protocol was approved by an Institutional Review Committee (DEC) for the use of animals.

Animals were provided under Isoflurane anaesthesia (4.5% for induction and 2.5–3.0% for maintenance) and administration of atropine sulphate (0.1 ml atropine im) with a standard EEG-electrode (Plastic Products, MS 333 2-A). Electrodes were placed on the surface of the cortex, one in the frontal region (coordinates with the skull surface flat and bregma 0; A 2; L −3.5), and the second one in the parietal region (area 17, A −6.0; L −4.0). The ground electrode was placed in the cortex of the cerebellum. We did not perform any histology since the electrodes were placed only on the surface of the cortex. Following surgery, rats were allowed to recover for at least one week.

Before the experiment started, the rats were put into transparent recording cages (25 × 25 × 35 cm), connected to EEG leads, and were habituated to the experimental conditions for 16 h. Progesterone (Sigma) was dissolved in a 20% 2-hydroxypropyl-β-cyclodextrin (CD; Sigma) whereas finasteride {[4-azaandrost-1-ene-17-carboxamide,*N*-(1,1-dimethylethyl)-3-oxo-,(5a,17b)]; Steraloids} was suspended in 1% of Tween-80. The drugs were injected in a volume of 2 ml/kg. Animals were injected with progesterone (10 and 20 mg/kg ip) or CD after a 1-h baseline EEG recording in the progesterone dose-response experiment, and the EEG was recorded for a 2-h postinjection period. The dose of 10 mg/kg was chosen, because similar dose (8 mg/kg) was reported to increase progesterone and allopregnanolone level in whole brain up to 6 and 4 ng/g, respectively (Frye and Scalise, 2000). However, we tested also the dose of 20 mg/kg since progesterone and allopregnanolone brain concentrations are, under certain conditions such as pregnancy and stress, much higher than those mentioned above (Concas et al., 1999). In finasteride/progesterone experiment, after 1-h baseline EEG recording, animals were injected with finasteride (50 mg/kg sc) or 1% Tween-80 and after 2-h postdrug EEG recording, progesterone (20 mg/kg ip) or CD were administered and EEG was recorded for the next 2 h. The dose of 50 mg/kg of finasteride was found to significantly decrease allopregnanolone level in rat brain and the maximum effect was observed at 2 h after its administration (Frye and Walf, 2002, Concas et al., 1998). During the 1-day finasteride EEG study, the cortical EEGs were continuously recorded after administration of finasteride (50 mg/kg sc) or 1% Tween-80.

The EEGs were amplified, filtered between 1 and 100 Hz, digitised at 200 samples/s and stored on a compact disk for off line analyses. Counted were the number of trains of SWD. The EEG analysis was facilitated by an automatic routine, which searched for the presence of high voltage activity with a minimal duration of 1 s (Westerhuis et al., 1996). By this routine, the selected periods of aberrant EEG activity were visually inspected and scored by a trained EEG analyst according to criteria elaborated earlier (Van Luijtelaar and Coenen, 1986).

During the first hour after progesterone, finasteride or appropriate vehicle administration the behavior of the rats was closely observed for 30 min, through a window from an adjacent room. Explorative (sniffing, rearing, locomotor behavior), automatic (grooming, eating, drinking) and passive behavior (sitting or lying motionless) was scored according to criteria described earlier (Van Luijtelaar et al., 1996). Data were stored on a Tandy 102 and off-line analysed with the aid of The Observer (Noldus, 1991).

The results are presented as mean ± S.E.M. All the data were statistically analysed by ANOVAs with drugs or dose

as between-group factor and time (hours) as within-group factor, followed, if appropriate, by univariate analyses (dose or drug as between-group factor) and by Duncan's multiple range tests for comparisons between groups. For all tests, a P level of .05 was considered to represent a significant difference.

3. Results

3.1. Effects of progesterone on the number, mean and total duration of SWD

The results are presented in Table 1. The ANOVA showed an hour effect [$F(2,21)=4.31$, $P<.05$], a dose effect [$F(2,21)=3.48$, $P<.05$] and an Hour × Dose interaction effect [$F(4,42)=2.70$, $P<.05$] for the number of SWD. An hour effect [$F(2,40)=4.20$, $P<.05$] was also found for the total duration of SWD. There was no difference between the three groups before the injection (univariate analyses of variance), but after injection there was a dose effect in the first hour on number of SWD. Post hoc tests (Duncan's multiple range tests) showed that progesterone 20 mg/kg had a significant effect. The number of SWD was higher after progesterone in 20 mg/kg dose than after 10 mg/kg or vehicle (CD). There was also a nonsignificant increase after 20 mg/kg progesterone in the second hour postinjection. In all, progesterone increased the number of SWD but only during the first postinjection hour.

3.2. Effects of finasteride on progesterone-induced increase in number of SWD

The results are presented in Table 2 and in Fig. 1. First it was analyzed whether finasteride had any effect on SWD. The ANOVA and post hoc tests (Duncan's multiple range tests) showed that finasteride 50 mg/kg alone has no significant hour and dose effect on the number, total and mean duration of SWD.

Table 1
Effects of progesterone (Prog) on number, total and mean duration of SWD during baseline (B) and postinjection hours (1 and 2)

Treatment	Hour	Number of SWD	Total duration of SWD	Mean duration of SWD
CD	B	18.1 ± 2.9	123.9 ± 25.8	6.6 ± 0.8
Prog-10 mg/kg	B	25.9 ± 2.6	200.7 ± 30.5	7.1 ± 0.4
Prog-20 mg/kg	B	17.5 ± 2.6	125.7 ± 25.6	6.8 ± 0.8
CD	1	22.8 ± 3.4	174.2 ± 35.6	7.2 ± 0.5
Prog-10 mg/kg	1	35.1 ± 3.5	211.7 ± 16.9	6.2 ± 0.5
Prog-20 mg/kg	1	45.0 ± 9.2*	310.9 ± 102.6	6.1 ± 0.6
CD	2	19.0 ± 3.0	132.9 ± 29.2	6.7 ± 0.7
Prog-10 mg/kg	2	28.1 ± 3.5	177.1 ± 34.7	6.0 ± 0.7
Prog-20 mg/kg	2	31.3 ± 6.41	194.7 ± 61.4	5.7 ± 0.4

CD is cyclodextrine which was used as solvent.
Mean ± S.E.M. are given; total and mean duration in seconds.
* $P<.05$ vs. vehicle-treated group.

Table 2
Effects of finasteride (Fin), progesterone (Prog) and combination of finasteride and progestone administration on number, total and mean duration of SWD

Treatment	Hour	Number of SWD	Total duration of SWD	Mean duration of SWD
(Veh)	B	21.1 ± 4.0	159.0 ± 36.7	6.8 ± 1.0
(Fin-50 mg/kg)	B	19.1 ± 3.0	132.5 ± 24.1	7.8 ± 1.3
(Prog-20 mg/kg)	B	17.6 ± 4.8	134.0 ± 41.3	8.0 ± 0.8
(Fin + Prog)	B (fin or tween)	23.4 ± 4.4	182.0 ± 40.6	7.0 ± 1.0
Veh	1	20.0 ± 3.9	128.0 ± 30.3	5.8 ± 0.8
Fin-50 mg/kg	1	29.2 ± 4.3	181.1 ± 38.1	5.9 ± 0.6
Veh (Prog-20 mg/kg)	1	27.6 ± 5.5	255.0 ± 51.0	6.8 ± 0.3
Fin (+ Prog)	1	31.1 ± 3.2	205.3 ± 25.4	6.5 ± 0.4
Veh	2	19.4 ± 3.6	113.0 ± 24.7	5.1 ± 0.7
Fin-50 mg/kg	2	20.7 ± 2.1	116.7 ± 12.9	5.7 ± 0.5
Veh (Prog-20 mg/kg)	2	25.1 ± 4.1	178.8 ± 35.8	7.0 ± 0.4
Fin (+ Prog)	2 (prog or CD)	22.0 ± 3.1	135.3 ± 26.5	5.7 ± 0.4
Veh + CD	3	26.0 ± 4.3	142.0 ± 25.3	5.0 ± 0.5
Fin-50 mg/kg + CD	3	26.6 ± 1.4	154.1 ± 18.2	5.7 ± 0.4
Veh + Prog-20 mg/kg	3	44.3 ± 9.3*	304.0 ± 66.8**	6.6 ± 0.3
Fin + Prog	3	27.4 ± 2.3#	163.8 ± 15.4#	6.0 ± 0.4
Veh + CD	4	16.6 ± 3.0	81.5 ± 18.0	4.6 ± 0.5
Fin-50 mg/kg + CD	4	14.8 ± 2.5	87.8 ± 20.5	5.5 ± 0.6
Veh + Prog-20 mg/kg	4	25.0 ± 7.5	154.0 ± 71.0	5.7 ± 0.7
Fin + Prog	4	19.3 ± 2.5	117.4 ± 19.6	5.8 ± 0.4

Mean ± S.E.M. are given; total and mean duration in seconds. Conditions between brackets indicate that the substance was not given yet. B-baseline hour; 1, 2—first and second hours after finasteride injection; 3, 4—first and second hours after progesterone administration.
* $P<.05$ vs. vehicle-treated group.
** $P<.01$ vs. vehicle-treated group.
# $P<.05$ vs. progesterone-treated group.

A second ANOVA on the data in which progesterone was given showed a significant drug effect on the number [$F(3,32)=3.58$, $P<.05$] and total duration [$F(3,31)=4.82$, $P<.01$] of SWD. Post hoc tests showed that progesterone at a dose of 20 mg/kg enhanced the number and total duration of SWD, but not the mean duration of SWD.

Pretreatment with finasteride 50 mg/kg blocked the effect of progesterone 20 mg/kg on the number [$F(1,16)=4.62$, $P<.05$] and total duration [$F(1,16)=6.30$, $P<.05$] of SWD. Finasteride 50 mg/kg was ineffective itself but blocked the effect of progesterone 20 mg/kg during the first postinjection hour.

3.3. Long-term effect of finasteride on SWD

The results are presented in Fig. 2. The ANOVA showed a time effect [$F(24,150)=3.01$, $P<.001$] for number of SWD and for total duration [$F(24,150)=2.66$,

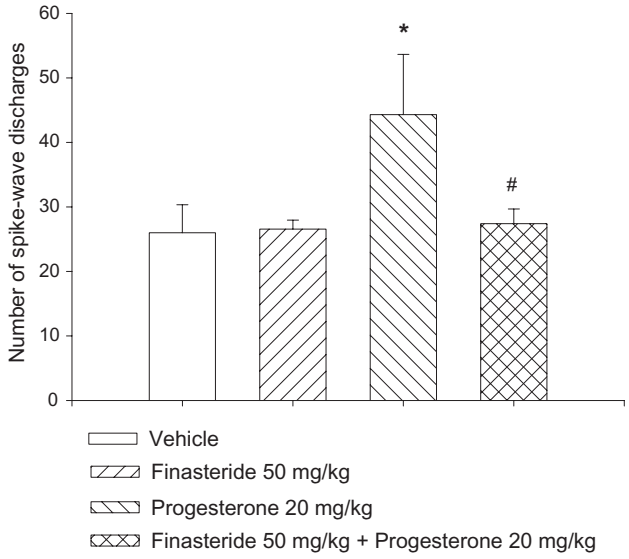

Fig. 1. Effects of finasteride on progesterone-induced increase in number of SWD during the first hour after progesterone injection. Mean ± S.E.M. are given. * $P < .05$ vs. vehicle-treated group; # $P < .05$ vs. progesterone-treated group.

$P < .001$] but not for mean duration of SWD. Post hoc tests (Duncan's multiple range tests) showed a significant time effect: the number and total duration of SWD were different for the various hours and showed a circadian distribution with the maximum in the first hour of the EEG recording period, during the dark period (at the 4th–5th h of the dark period) and a minimum in the 8th to the 10th h of the EEG registration period, at the beginning of the light period (real clock time—19–21) in agreement with previous results (van Luijtelaar and Coenen, 1988). Injection of finasteride 50 mg/kg did not significantly change the number, total and mean duration of SWD at any hour in comparison with vehicle.

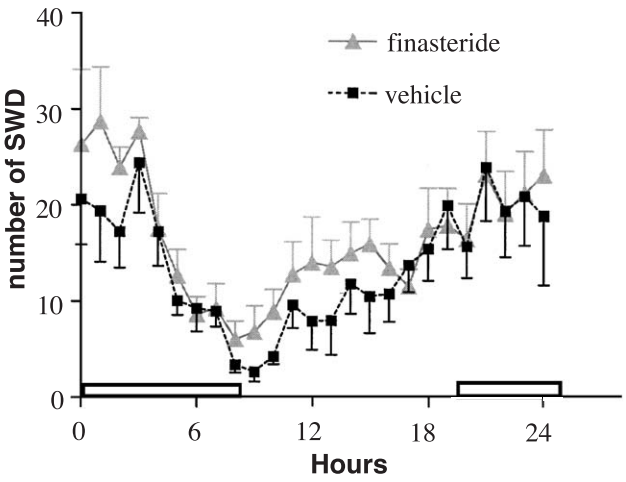

Fig. 2. Effect of finasteride on the distribution of SWD within the 24-h period. Mean ± S.E.M. are given. Dark period is indicated by black squares on the *X*-axis.

Table 3
Effects of progestone, finasteride and combination of finasteride and progestone on behaviour during the recording period

Treatment	Exploratory	Automatic	Passive
CD	593 ± 123	460 ± 94	747 ± 139
Prog-10 mg/kg	582 ± 82	394 ± 62	824 ± 104
Prog-20 mg/kg	529 ± 116	580 ± 111	691 ± 153
Veh	456 ± 84	593 ± 107	752 ± 156
Fin-50 mg/kg	482 ± 83	565 ± 89	754 ± 121
Veh	516 ± 90	508 ± 108	776 ± 160
Prog-20 mg/kg	384 ± 65	471 ± 95	946 ± 125
Fin + Prog	491 ± 102	447 ± 82	863 ± 144

Data (mean ± S.E.M.) in seconds.

3.4. Effects of progesterone, finasteride and combined administration on behavior

The ANOVAs and the post hoc test (Duncan's multiple range tests) showed no significant effects of progesterone or differences between the groups that have received finasteride (50 mg/kg) or progesterone (20 mg/kg) in the number and total time of exploratory, automatic and passive behavior (Table 3). Also in animals pretreated with finasteride 50 mg/kg and next injected with progesterone 20 mg/kg no changes in behavior were observed (data not shown).

4. Discussion

The main finding of the present study is the antagonism of finasteride—an inhibitor of 5α-reductase—towards the effect of progesterone on absence seizures in WAG/Rij rats. The microsomal enzyme 5α-reductase exists in two isoforms (types I and II). Both isoforms can be found in the brain of the rat, however a higher concentration of type I can be found in brain tissue (Mensah-Nyagan et al., 1999). Finasteride is a potent inhibitor of both types of 5α-reductase in rodents and the dose and time of its administration in this study has been shown to be effective (Concas et al., 1998; Frye et al., 1998a,b). Genomic action of progesterone on SWD was excluded previously (Van Luijtelaar et al., 2001), but nongenomic progesterone action can result not only from action of allopregnanolone, but also from modulation by progesterone some membrane receptors. However, the fact that finasteride completely blocked effect of progesterone on SWD, indicated, that not progesterone itself, but its metabolite produced by 5α-reductase is involved in modulation of absence epilepsy. Activity of 5α-reductase shows age-related increase in both male and female rat brains (Stuerenburg et al., 1997), which correlates with development of SWDs in genetic models of absence epilepsy. Finasteride inhibits not only production of allopregnanolone, but also its direct precursor dihydroprogesterone. However, since the latter compound shows a weak affinity towards $GABA_A$ receptors it is more likely that allopregnanolone plays the main role in regulation of SWDs.

Finasteride alone had no significant effect on spontaneous SWD in WAG/Rij rats, which is in line with outcomes of studies of others, who showed that this 5α-reductase inhibitor, at similar dose, did not affect pentylenetetrazol-induced seizures, although it blocked the anticonvulsant effect of progesterone in this model (Kokate et al., 1999). Other authors reported that finasteride given alone had significant effect on seizures induced by perforant pathway stimulation in condition mimicking estrous (Frye and Scalise, 2000). This underlines difference in susceptibility of convulsive and nonconvulsive seizures to endogenous neuroactive steroid regulations. The lack of effect of finasteride on spontaneous SWD observed throughout 24 h following this drug injection suggests that the conversion of endogenous progesterone to allopregnanolone plays only a small role in the regulation of absence seizures in male rats under basal conditions. However, it should be kept in mind that 5α-reductase is involved not only in conversion of progesterone to 5α-dihydroprogesterone, but also in the conversion of deoxycorticosterone (DOC) and testosterone to 5α-dihydroderivatives, which are further converted to neuroactive steroids—$GABA_A$ agonists e.g., allotetrahydrodeoxycorticosterone (THDOC) and 5α-androstane-3α, 17β-diol, respectively. It has been demonstrated that THDOC and 5α-androstane-3α, 17β-diol inhibit convulsive seizures (Frye and Reed, 1998; Reddy and Rogawski, 2002) but their putative involvement in absence epilepsy has not been the subject of an experimental study yet. It is known however that castration in male WAG/Rij rats enhanced the total duration of SWD and from this it can be inferred that testosterone may reduce SWD (Van Luijtelaar et al., 1996). Castrated males may have lower brain levels of some testosterone-derivated neuroactive steroids, which involvement in regulation of SWD have not been investigated as yet.

Although in basal condition finasteride did not affect SWD, one may expect that under stress condition, where the production of allopregnanolone as well as THDOC is increased, the effects of finasteride could be demonstrated. Indeed, Reddy and Rogawski (2002) showed that finasteride reverses the anticonvulsive effect of swim stress in male rats. Similarly, one can speculate that in physiological states, such as at the proestrus day of estrous cycle in female rats, when high level of progesterone and allopregnanolone correlates with increase of SWD, inhibition of 5α-reductase might attenuate the number of SWD. Indeed, in adult rat brain the concentration of progesterone and allopregnanolone in females (diestrous, metestrous) and in males are similar (Kellogg and Frye, 1999). At the proestrus day of the estrous cycle the levels of progesterone and allopregnanolone are at least threefold higher and in that day an increase in SWD was observed (Kellogg and Frye, 1999; Van Luijtelaar et al., 2001).

Progesterone, as well as finasteride or combined administration of finasteride and progesterone, did not affect behaviour under the circumstances of our study. Therefore, the changes in number and total duration of SWD cannot be ascribed to behavioural changes.

The present data indicate that progesterone enhances SWD not only in female WAG/Rij rats (Van Luijtelaar et al., 2001), but also in males. However, in our previous study, when female rats were used, the effect of progesterone on SWD seemed to be stronger than in males in the present study. Progesterone (20 mg/kg) increased number of SWD by twofold in male rats (present study), while by fourfold in female rats (Van Luijtelaar et al., 2001). This difference is rather not connected with density or distribution of progesterone receptors in the brain of female and male rats, since progesterone-induced enhancement of SWD is independent on intracellular progesterone receptors (Van Luijtelaar et al., 2001). Furthermore, since the brain levels of enzymes involved in transformation of progesterone to allopregnanolone (e.g., 5α-reductase type I and 3α-hydroxysteroid oxidoreductase type II) are similar in both sexes, so stronger effect of progesterone in female is rather unlikely to result from difference in progesterone metabolism. The stronger effects of progesterone in females may be rather due to higher sensitivity of $GABA_A$ receptors to the metabolite of progesterone—allopregnanolone. This assumption is supported by some studies that indicate sex-specific differences in $GABA_A$ receptor kinetics (Smith et al., 1996) and stress-induced changes in the $GABA_A$/benzodiazepine receptor complex (Wilson and Biscardi, 1994). Additionally, less potent effect of progesterone in male rats can results from higher amount of all neurosteroids—positive modulators of $GABA_A$ receptors—in brain of male rats, which might decrease the sensitivity of $GABA_A$ receptors. For example, the concentration of 5α-androstane-3α, 17β-diol is ca. tenfold higher in the brain of adult male compared to female rats.

In summary, progesterone enhances SWD in male WAG/Rij rats, although to a lesser extent than in females. The results provide evidence that the effects of progesterone on SWD depend on 5α-reductase activity, and synthesis of allopregnanolone, a $GABA_A$ agonist.

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