ELSEVIER

Pharmacology, Biochemistry and Behavior 74 (2002) 103–109

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Effects of ovariectomy and estradiol on acoustic startle responses in rats

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Received 20 March 2002; received in revised form 24 June 2002; accepted 17 July 2002

Abstract

Long-term (3 months) ovariectomized (OVX) rats were used to model hormone withdrawal as occurring in menopause. We previously reported alterations in brain dopamine (DA), GABA and serotonin receptors following ovariectomy in this model. To assess the functional effect of these biochemical changes, we compared rats that were intact, OVX and OVX-treated with 17β-estradiol (E_2; OVX + E_2) for 2 weeks on measures of their acoustic startle responses (ASR) and prepulse inhibition (PPI) of acoustic startle. The effects of a mixed D_1/D_2 dopaminergic agonist, apomorphine (APO; 0.25, 0.5 and 0.75 mg/kg sc) were tested on ASR and PPI of acoustic startle. Without APO, all groups of rats showed no difference in baseline ASR or PPI of acoustic startle. Following administration of APO (0.25, 0.5 and 0.75 mg/kg), ASR was significantly increased in OVX rats compared to intact rats and this was corrected with E_2 treatment. In all groups of animals, APO decreased PPI of acoustic startle. APO disrupted PPI to a lesser extent in OVX animals with or without E_2 treatment compared to intact rats. However, when group differences in APO-induced ASR were statistically controlled for, there were no longer any differences in APO disruption of PPI among the three treatment groups. These results indicate that long-term ovariectomy has persistent effects on the modulation of ASR, and these effects can be at least partly corrected with E_2 replacement therapy.

Keywords: Acoustic startle; Dopamine; Estradiol; Menopause; Ovariectomy; Prepulse inhibition

1. Introduction

Estrogens have been shown to exert profound effects on brain differentiation, neural plasticity and central neurotransmission during development (Kawata, 1995; McEwen and Alves, 1999). In adult men and women, accumulating evidence supports a modulatory role for these steroids in the brain and more recently, their prime importance in the normal maintenance of brain function during ageing (Cyr et al., 2000; Simpkins et al., 1994). With increased life expectancy and the average age of menopause remaining constant, women can expect to live up to one half of their adult lives after menopause (Vliet and Davis, 1991). Women represent more than half of the population and more than 60 million women throughout the world now use oral contraceptives (Tierney and Luine, 1997). Furthermore, the recent determination that long-term use of oral contraceptives is safe, the lower steroid concentrations now used and their reported safety for women over the age of 35 years (Tierney and Luine, 1997) create a situation that could be used to improve drug treatment and perhaps find new applications for gonadal steroids as drugs for the brain.

We have previously used ovariectomized (OVX) rats to model gonadal hormone withdrawal occurring at menopause, and have shown a decrease of dopamine (DA) D_1 and D_2 receptors in brain areas such as the frontal cortex and striatum, in rats OVX for 3 months (Bossé and Di Paolo, 1995, 1996). The decrease in D_2, but not in D_1 receptors, is corrected with 2 weeks of estradiol treatment. The striatal DA transporter has also been shown to decrease progressively with time after ovariectomy and to lose its response to estradiol replacement therapy in the long-term (3 months) (Bossé et al., 1997). Moreover, we have shown decreases in serotonin 2A ($5\text{-}HT_{2A}$) receptors in frontal cortex, striatum, dorsal raphe nucleus and frontoparietal cortex in long-term OVX rats and these receptor changes can be corrected with

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PII: S0091-3057(02)00967-X

an estradiol treatment (Cyr et al., 1998). By contrast, the benzodiazepine site associated with the $GABA_A$ receptor increases in long-term OVX rats in the striatum, nucleus accumbens (Nacc), entopeduncular nucleus and the substantia nigra and this is also corrected with an estradiol treatment (Bossé and Di Paolo, 1996). However, in the globus pallidus, the benzodiazepine site is decreased in OVX compared to intact rats and this is also corrected with estradiol treatment (Bossé and Di Paolo, 1996). Hence, long-term ovariectomy has a wide spread effect on several neurotransmitter systems and brain areas, which together may lead to a novel equilibrium in the brain and altered functional responses.

Given the effects of OVX and estradiol on DA receptors and transporters, we hypothesized that DA-mediated behavioural responses might be altered by long-term OVX. Prepulse inhibition (PPI) of the acoustic startle response (ASR) is a behavioural response well documented to be modulated by central dopaminergic neurotransmission. The ASR is a short-latency reflex behaviour that is elicited by a brief, intense acoustic pulse, while PPI is the reduction of the acoustic startle that is observed when the startling pulse is preceded by a weak prepulse (Hoffman and Ison, 1980). PPI is a cross-species phenomenon, which occurs normally in humans and experimental animals. Deficits in PPI have been demonstrated in persons suffering from a number of mental and neurological disorders including schizophrenia, obsessive–compulsive disorder, attention deficit disorder and Tourette's syndrome (for review, see Swerdlow and Geyer, 1998; Swerdlow et al., 2000) and has been used to model deficiencies in sensorimotor gating thought to occur in these disorders. A role for dopaminergic modulation of PPI is supported by extensive experiments indicating that PPI is disrupted by dopaminergic agonists such as apomorphine (APO) and amphetamine, effects that are reversed by DA antagonists (for review, see Swerdlow and Geyer, 1998; Swerdlow et al., 2000). Moreover, the ability of DA antagonists, to prevent APO disruption of PPI in rats seems to correlate with their antipsychotic potency in humans (Swerdlow et al., 1994). PPI is disrupted by direct infusion of DA or DA agonists into the Nacc or anteromedial striatum (Swerdlow et al., 1992; Wan et al., 1994), or by 6-hydroxydopamine-induced depletion of DA in the medial prefrontal cortex (Bubser and Koch, 1994). Stimulation of the dopaminergic system via blockade of the DA transporter, like direct agonists, also disrupts PPI in rodents (Dulawa and Geyer, 1996; Mansbach et al., 1988). This profile suggests that PPI might also be altered by the DA receptor changes that have been observed in OVX rats.

Gonadal hormones have been reported to influence PPI of acoustic startle in humans (Abel et al., 1998; Swerdlow et al., 1993, 1997, 1999), with greater levels of PPI in males compared to females, and variation in PPI across the menstrual cycle in females. In rats, PPI has been reported to be reduced in females during proestrus compared to diestrous or oestrous or compared with male rats (Koch, 1998), although no male/female differences in PPI have been observed in studies with female rats tested at random phases of the oestrous cycle (Swerdlow et al., 1993). These differences may arise in part from the impact of reproductive hormones on brain substrates regulating PPI (Koch, 1999; Rupprecht et al., 1999; Swerdlow et al., 1997). Given this background, the present study investigated whether long-term ovariectomy and estradiol replacement in rats affect ASR and PPI of acoustic startle, and the dopaminergic modulation of these behavioural responses by APO.

2. Materials and methods

2.1. Animals

All procedures concerning the use of animals were strictly in accord with the guidelines of the Canadian Council on Animal Care and were approved by the Laval University and McGill University Animal Care Committees. Forty-six adult Sprague–Dawley female rats, weighing 250–350 g, were purchased from Charles River Canada (St-Constant, Québec, Canada). The animals were housed two per cage and maintained at 22–23 °C on an artificial day/night cycle (light on from 05:00 to 19:00 h). They received rat chow and water ad libitum. Female rats were OVX under anaesthesia (1.5% halothane/air mixture). Three groups of animals were included in the experiment: (i) 15 rats that had been OVX and maintained for at least 3 months (long-term ovariectomy; OVX); (ii) 16 rats OVX, maintained for at least 3 months and receiving estradiol treatment (17β-estradiol (E_2), 10 μg sc, twice daily, OVX + E_2); (iii) 15 intact female rats at random stages of the oestrous cycle (intact). Steroid and vehicle treatments were started 2 weeks before the beginning of the behavioural testing and were maintained throughout the entire behavioural test period. Both OVX rats without E_2 therapy and intact rats received vehicle injections (0.3% gelatin in saline solution, twice daily). Data from all 46 rats (15 OVX, 16 OVX + E_2, 15 intact) were included in the analyses of ASR and PPI responses.

2.2. Drugs

Apomorphine hydrochloride (APO) was obtained from Research Biochemicals International (Natick, MA, USA) and was dissolved in 0.9% saline containing 0.1% ascorbic acid. APO at 0.25, 0.5 or 0.75 mg/kg and saline/ascorbic acid vehicle were administered subcutaneously in a volume of 1 ml/kg.

2.3. ASR and PPI of acoustic startle

Startle reactivity was measured using two SR-LAB startle apparatuses (San Diego Instruments, San Diego, CA, USA). Each consisted of a clear Plexiglas chamber

(8-cm diameter, 16 cm long), resting on a platform within a lit, sound-attenuated and ventilated enclosure. A piezoelectric transducer detected the vibrations caused by movement of the animal and transduced the startle response. A SR-LAB calibration unit was used to produce consistent response sensitivity between chambers and across days of testing. A speaker located in the ceiling of the chamber produced continuous background white noise at 70 dB and the required acoustic stimuli. Sound intensity within the chambers was calibrated using a Radio Shack digital sound level meter (A scale). A microcomputer control unit digitized and stored startle responses and also controlled timing and presentation of acoustic stimuli.

Startle testing took place between 8:00 and 17:00 h. The startle session began with a 5 min acclimatisation period in the presence of 70 dB background noise, which continued throughout the session. After this habituation period, the animals were presented with two orienting startle pulses (120 dB, 30 ms broad band burst) to test basal startle responsiveness. Data from these two pulses were discarded, as the animals generally displayed exaggerated startle amplitudes on these trials relative to startle trials occurring later in the session. Next, five blocks of trials were delivered. Each of these blocks consisted of the following eight trials: two startle pulse trials (pulse-alone), five different prepulse + pulse trials and one no-stimulus trial. The pulse-alone trial consisted of a 120-dB pulse for 30 ms. The five prepulse + pulse trials consisted of a 30-ms prepulse at 3, 6, 9, 12 or 15 dB above background noise (70 dB) followed by a 70-ms delay and then a startle pulse (120 dB, 30 ms). These 40 trials were randomly presented, with the restriction that no more than two trials of the same type could occur in succession. The intertrial interval was a variable interval schedule with an average of 15 s (range 10–20 s). Startle amplitude was defined as the average of 100 readings taken at 1-ms intervals, beginning at stimulus onset. Total length of session was 15 min.

Two weeks after testing for baseline PPI, all animals were tested for effects of saline and APO (0.25, 0.5 and 0.75 mg/kg) on ASR and PPI. Different doses of APO or saline were administered in a counterbalanced order within each group to minimise carryover effects, with an interval of 10 days between each drug (or saline) treatment. APO or saline was injected 10 min before the animal was placed in the startle apparatus and tested for ASR and PPI using the protocol described above.

ASR was defined as the mean startle amplitude averaged from the final 10 pulse alone trials. %PPI at each of the prepulse intensities was calculated according to the following formula: $[(\text{STARTLE} - \text{PPI})/\text{STARTLE}] \times 100$, where STARTLE was the mean startle amplitude from the final 10 pulse alone trials, and PPI was the mean startle amplitude for the five trials at each prepulse intensity.

2.4. Data analysis

Data for baseline ASR and for effects of saline vehicle on ASR were analyzed using one-way ANOVA with group condition as between-subject-factor. ASR after saline for each animal, as an estimate of effects of vehicle injection, was subtracted from ASR after APO for that animal, to yield values for APO-induced ASR. Data for APO-induced ASR were analysed using two-way ANOVA with group condition as between-subject-factor and APO dose as within subject repeated measure. Data for baseline PPI and for PPI after saline were analysed using two-way ANOVA with group condition as between-subject factor and prepulse intensity as within subject repeated measure. Data for effects of APO on PPI were analysed using three-way ANOVA with group condition as a between-subject-factor and APO dose and prepulse intensity as within subject repeated measures. Significant interactions were decomposed with simple main effect F-tests. Post-hoc pairwise comparisons were conducted using Tukey's HSD tests. The accepted level of statistical significance was $P < .05$.

3. Results

The mean baseline ASR in intact, OVX and OVX + E_2 rats were not significantly different [$F(2,46) = 1.38$, $P = .262$, Table 1]. One-way ANOVA showed a significant effect of group on body weight [$F(2,46) = 33.35$, $P < .0001$, Table 1]. However, these differences in body weight did not significantly alter ASR at baseline, and baseline ASR did not correlate with weight across the three experimental groups. ASR after injection of saline vehicle were also not significantly different in intact, OVX and OVX + E_2 rats [$F(2,46) = 2.16$, $P = .126$, Table 1].

Fig. 1 shows ASR after administration of three different doses (0.25, 0.5 and 0.75 mg/kg) of the D_1/D_2 agonist, APO. ASR after saline for each animal, as an estimate of injection effects, has been subtracted from ASR after APO to yield the values for APO-induced ASR analyzed in Fig. 1. Alternative analysis of ASR after APO as a percentage of ASR after saline yields similar results to those described. Two-way ANOVA showed significant main effects for

Table 1
Effects of long-term ovariectomy (OVX) and 17β-estradiol (E_2) therapy in rats on body weight and on ASR at baseline and after saline injection

Measure	Intact	OVX	OVX + E_2
Body weight	307 ± 8	433 ± 15 *	348 ± 8 *,#
ASR at baseline	51.6 ± 6.3	74.4 ± 13.3	84.3 ± 16.5
ASR after saline injection	43.5 ± 4.6	54.2 ± 7.0	60.2 ± 5.4

Body weight is expressed as mean ± S.E.M. in grams. ASR is expressed as mean ± S.E.M. startle amplitude in arbitrary startle units produced by 120 dB pulses in intact, OVX or OVX rats with 17β-estradiol therapy (OVX + E_2).

* $P < .01$ vs. intact.

\# $P < .01$ vs. OVX.

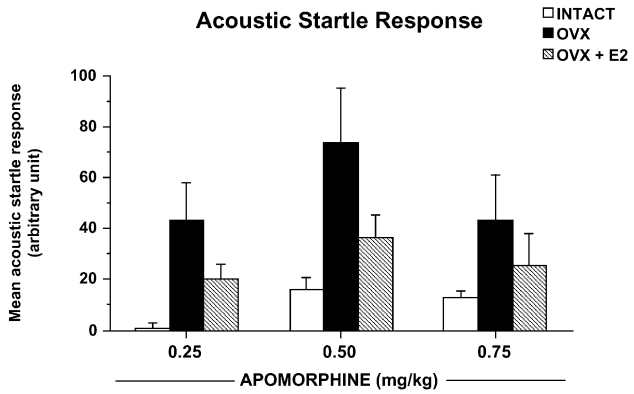

Fig. 1. Effect of ovariectomy and 17β-estradiol therapy on APO modulation of ASR in rats. Rats remained intact (INTACT) or were OVX 3 months prior to behavioural testing. Two weeks prior to and during testing, OVX rats received twice daily subcutaneous injections of vehicle (OVX group) or 17β-estradiol (10 μg, OVX + E_2 group). Data show acoustic startle amplitudes produced by 120 dB pulses (in the absence of any prepulse) in INTACT, OVX or 17β-estradiol-treated OVX rats after a subcutaneous injection of 0.25, 0.5 or 0.75 mg/kg APO. Results are expressed as mean ± S.E.M. startle amplitude, produced by 120 dB pulses (in the absence of any prepulse). ASR after saline for each animal, as an estimate of injection effects, has been subtracted from the ASR after APO to yield the values for APO-induced ASR shown.

group [$F(2,46) = 8.92$, $P = .005$] but no effect of APO dose [$F(2,92) = 0.54$, $P = .585$] and no significant Group × Dose interaction [$F(4,92) = 0.26$, $P = .903$]. Tukey's tests on the group main effect revealed that ASR in OVX rats was significantly greater than the response in intact rats ($P < .01$). ASR in OVX + E_2 animals was significantly different ($P < .05$) from ASR in OVX animals and not significantly different from ASR in intact animals. This indicates that the enhanced APO-induced ASR observed in OVX animals is reversed by E_2 replacement. Inspection of Fig. 1 suggests that the reversal by E_2 may be only partial, even though APO-induced ASR is not statistically different in intact versus OVX + E_2 groups.

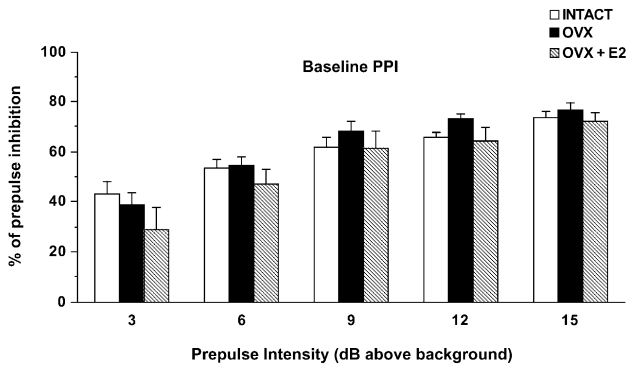

Fig. 2. Effect of ovariectomy and 17β-estradiol therapy on PPI of acoustic startle. INTACT, OVX or OVX rats with 17β-estradiol therapy (OVX + E_2) were tested for PPI of acoustic startle, under basal (no injection) conditions. Results show the mean percentage (± S.E.M.) of PPI produced at various prepulse intensities (3, 6, 9, 12 or 15 dB above background).

Fig. 2 compares PPI under basal (no injection) conditions in intact, OVX and OVX + E_2 rats. Under basal conditions, two-way ANOVA showed a significant effect of prepulse intensity [$F(4,184) = 65.33$, $P < .0001$], but no significant effect of group [$F(2,46) = 1.07$, $P = .353$] and no Group × Prepulse Intensity interaction [$F(8,184) = 0.99$, $P = .443$]. Thus, neither OVX nor OVX with E_2 replacement had any significant effect on baseline PPI compared to intact rats.

The effects of saline injection and of APO (0.25, 0.5 and 0.75 mg/kg) on PPI in intact, OVX and OVX + E_2 rats are shown in Fig. 3. Two-way ANOVA of PPI after saline injection (Fig. 3a) showed a significant effect of prepulse intensity [$F(4,184) = 68.81$, $P < .0001$] but no significant

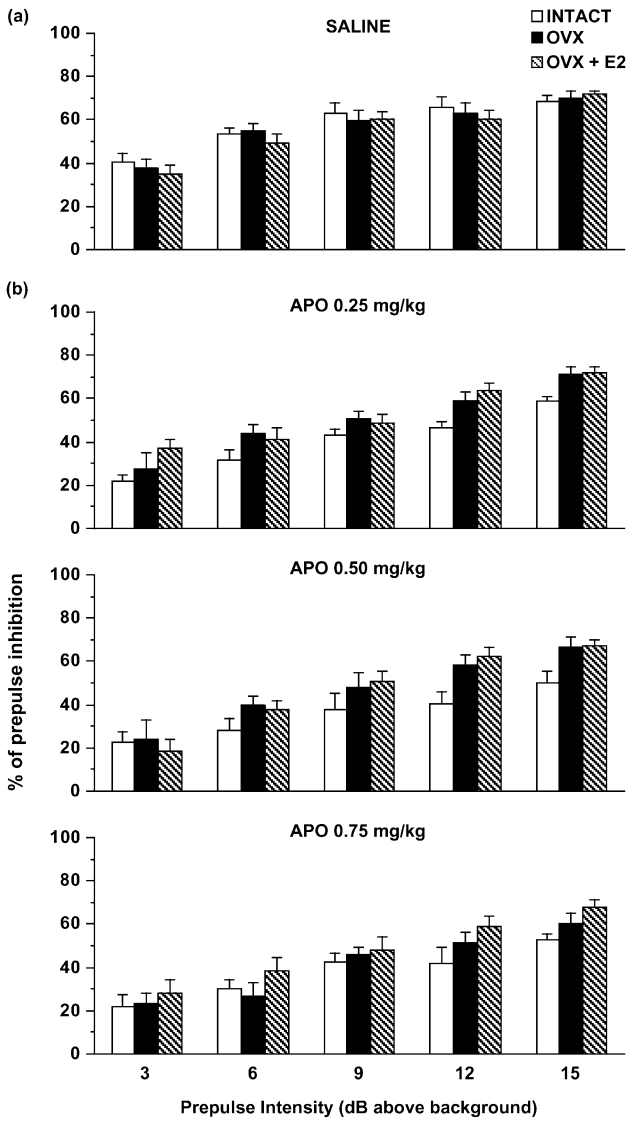

Fig. 3. Effect of ovariectomy and 17β-estradiol therapy on APO modulation of PPI of acoustic startle. INTACT, OVX or OVX rats with 17β-estradiol therapy (OVX + E_2) received subcutaneous injections of (a) saline or (b) 0.25, 0.5 or 0.75 mg/kg of APO, 10 min before testing for PPI. Results show the mean percentage (± S.E.M.) of PPI produced at various prepulse intensities (3, 6, 9, 12 or 15 dB above background).

effect of group [$F(2,46)=0.21$, $P=.814$] and no Group × Prepulse Intensity interaction [$F(8,184)=0.67$, $P=.717$]. Thus, PPI after saline injection was similar in the three groups of animals.

Three-way ANOVA of PPI after administration of APO (Fig. 3b) showed significant main effects for group [$F(2,46)=5.68$, $P=.006$] and for prepulse intensity [$F(4,184)=108.36$, $P<.0001$]. The main effect for APO dose was not significant [$F(2,92)=2.27$, $P=.109$] and no significant interactions were observed. Tukey's test on the group main effect revealed that APO disruption of PPI was significantly less in both the OVX ($P<.05$) and in the OVX + E_2 ($P<.01$) groups, compared to intact animals. Alternative analysis of the data with values for PPI after APO subtracted from values for PPI after saline, to correct for possible effects of saline injection in each animal, yields similar results. i.e., APO disruption of PPI was significantly less in the OVX + E_2 group compared to intact ($P<.01$), while the difference between OVX and intact animals just missed statistical significance ($P=.061$).

The diminished APO disruption of PPI in OVX animals, compared to intact animals, could theoretically be due to an enhanced excitatory effect of APO on ASR in the OVX animals. To assess this possibility, analysis of covariance was performed on data for PPI after APO, with ASR as covariate. This analysis revealed that, when differences in ASR are controlled for, there was no significant group difference in effects of APO on PPI and no significant interactions with group (P's>.05).

4. Discussion

The main finding of this study is that long-term OVX rats have persistent alterations in DA-mediated effects on ASR, and these alterations can be partly corrected with 2 weeks of E_2 replacement. Hence, APO, a mixed D_1/D_2 dopaminergic agonist, increased ASR in OVX compared to intact rats and this was corrected with an E_2 treatment. APO disrupted PPI in both intact and OVX animals and the APO disruption of PPI was less in the OVX groups with or without E_2 compared to the intact group. The present behavioural findings indicate that dopaminergic mechanisms in brain are affected by ovariectomy and are in accordance with our previous biochemical results (Bossé and Di Paolo, 1995, 1996).

Most of the work investigating DA and startle has focused on the phenomenon of PPI, however, various DA agents can modulate the basic startle reflex itself (i.e., ASR). The ASR activates a pathway involving the cochlear nucleus, ventrolateral pons, reticular formation and spinal motor neurons (Koch, 1999; Yeomans and Frankland, 1996). Reported effects of dopaminergic agents on ASR have not been completely consistent. For example, APO has been shown to decrease (Swerdlow et al., 1994) or have no effect on ASR (Feifel, 1999), while amphetamine increased ASR in some studies (Mansbach et al., 1988; Swerdlow et al., 1990) but not in others (Bakshi et al., 1995; Johannson et al., 1995). However, in general, systemic administration of drugs that increase dopaminergic neurotransmission, increase ASR (Koch, 1999; Meloni and Davis, 1999).

We observed that, compared to intact controls, OVX, but not OVX + E_2 animals, have increased ASR after APO treatment. While no mechanism is known whereby estrogens or progesterone might regulate ASR, there are known interactions (Becker, 1990; Di Paolo, 1994; Lindamer et al., 1997) between these hormones and dopaminergic substrates (Swerdlow and Geyer, 1998). We have previously shown in OVX rats, that D_1 and D_2 receptors are decreased in striatum and prefrontal cortex (Bossé and Di Paolo, 1995, 1996). These changes could contribute to the enhanced APO-induced ASR amplitude in OVX animals. The enhanced APO-induced ASR in OVX animals may be partly mediated via D_2 receptor changes since we have previously shown (Bossé and Di Paolo, 1996) that OVX-induced changes in D_2 receptors are reversed by E_2 treatment.

In addition to activating postsynaptic DA receptors, low doses of APO (<0.5 mg/kg) act on presynaptic DA receptors on dopaminergic terminals themselves to inhibit the release of endogenous DA. However, previous studies have shown that hormonal variations during the oestrous cycle or OVX have little effect on behaviour related to stimulation of presynaptic DA receptors (open field, stereotyped behaviour, body temperature, with the exception of grooming) (Diaz-Veliz et al., 1994; Kazandjian et al., 1987). This suggests a role for postsynaptic rather than presynaptic receptor mechanisms in mediating differential sensitivity to dopaminergic agents due to hormonal variation. Our study, however, cannot differentiate between pre- and postsynaptic mechanisms.

APO was significantly less effective in disrupting PPI in both OVX animals and the OVX + E2 group, compared to intact controls, although the magnitude of these group differences was not great. Apparent changes in PPI following an experimental manipulation may be due to changes in ASR (Davis, 1988). Thus, we considered the possibility that group differences in effects of APO on PPI in the current study could be due to group differences in effects of APO on ASR. After statistically controlling for effects of APO-induced ASR by analysis of covariance, group differences in APO-induced PPI were no longer observed. These analyses thus support the interpretation that diminished APO disruption of PPI in OVX (and in OVX + E_2) animals (i.e., overall greater PPI after APO compared to intact animals) may be due to enhanced APO-induced ASR in the OVX groups. The reason for this is not known. It may simply be that measurement of a greater degree of inhibition is facilitated when beginning with a higher ASR. It should be noted, however, that this contrasts to effects of strychnine, which enhances ASR but reduces PPI (Davis, 1988; Bakshi et al., 1995). Nonetheless, overall, it appears that the three treatment groups in the present study differ primarily with respect to their dopaminergic modulation of ASR

responses, rather than in dopaminergic modulation of PPI mechanisms.

An interesting finding of this study is that at baseline, intact, OVX and OVX + E_2 rats showed no difference in ASR or PPI of acoustic startle. This finding is consistent with a report showing that the magnitude of the ASR is not affected by gender or the phase of the oestrous cycle (Koch, 1998). Furthermore, as reported in the present study with long-term OVX, ASR and PPI of acoustic startle at baseline were recently shown not to be changed in 1-week OVX rats (Van den Buuse and Eikelis, 2001). Thus it appears that hormonal changes produced by OVX interact with dopaminergic mechanisms modulating ASR, but that these hormonal changes do not affect the basic mechanisms regulating baseline ASR or PPI. In 1-week OVX rats, startle amplitude was recently shown to be reduced at 30 min but not 18 h after estradiol treatment, whereas at both times estradiol induced a dose-dependent increase in PPI of acoustic startle (Van den Buuse and Eikelis, 2001). It is difficult to compare the latter study with our present results since the rats were OVX for a shorter period (1 week in Van den Buuse and Eikelis, 2001 compared to 3 months in the present study) and estradiol was investigated acutely (one injection investigated 30 min or 18 h after injection in Van den Buuse and Eikelis, 2001 compared to 2 weeks of twice daily injections in the present study). Indeed, we have previously shown different acute and chronic effects of estradiol on various measures of dopaminergic activity (Cyr et al., 2000; Di Paolo, 1994). Nevertheless, our findings and those of Van den Buuse and Eikelis (2001) overall indicate that estradiol influences ASR and PPI of acoustic startle in a complex manner likely involving several neurotransmitter systems.

In conclusion, this study showed enhanced sensitivity of OVX animals to the dopaminergic agonist, APO, when tested for effects on ASR, in comparison to intact rats. The diminished effect of APO on PPI in OVX animals may be largely due to the enhanced APO effect on ASR in these animals. These results suggest that long-term OVX has persistent effects on DA-mediated behavioural responses. Altered APO-induced ASR following OVX can be significantly corrected with 2 weeks of estradiol replacement therapy. Perhaps more complete reversal of OVX-induced changes in ASR requires replacement of the other major ovarian hormone, progesterone. Indeed, in male rats progesterone has been shown to reduce ASR and antagonize effects of APO on PPI (Rupprecht et al., 1999). These behavioural results, together with our previous biochemical findings, indicate that OVX rats constitute a useful model to study changes in neurotransmitter balance and behaviour occurring after menopause.

Acknowledgements

Supported by grants from the Canadian Institutes of Health Research (CIHR) to T.D.P., P.B. and J.R. C.V. held a postdoctoral fellowship from Fonds de la Recherche en Santé du Québec and M.C. held a studentship from CIHR.

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