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ScienceDirect
Pharmacology, Biochemistry and Behavior 88 (2008) 306–311
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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Rat strain differences in startle gating-disruptive effects of apomorphine occur with both acoustic and visual prepulses

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Received 6 July 2007; received in revised form 25 August 2007; accepted 31 August 2007
Available online 7 September 2007

Abstract

Prepulse inhibition of startle (PPI) is an operational measure of sensorimotor gating that is impaired in schizophrenia and is disrupted in rats by dopamine (DA) agonists like apomorphine (APO). Using acoustic prepulses and acoustic startle pulses, previous studies have demonstrated heritable strain differences between Sprague Dawley (SD) and Long Evans (LE) rats in the sensitivity to the PPI-disruptive effects of APO. As PPI deficits in schizophrenia are evident with both uni- and cross-modal stimuli, we tested whether strain differences in the gating-disruptive effects of APO occur with a cross-modal visual and acoustic stimulus combination. APO caused a dose-dependent disruption of both acoustic and visual PPI in SD rats. Compared to LE rats, SD rats were more sensitive to the PPI-disruptive effects of APO with both acoustic and visual PPI. These findings suggest that SD vs. LE strain differences in PPI APO sensitivity are mediated outside of the auditory system, within higher circuitry that regulates or processes multi-modal information. The present findings provide further validation for this heritable model of impaired sensorimotor gating in schizophrenia, which can be detected across multiple sensory modalities.

Keywords: Prepulse inhibition; Cross-modal; Apomorphine; Rat strain; Schizophrenia; Dopamine

1. Introduction

Evidence suggests that vulnerability for developing schizophrenia can be inherited (Harrison and Weinberger, 2005; Sullivan, 2005) and that genes conferring this vulnerability ultimately do so via changes in brain circuitry. Great effort is being put towards identifying the genetic basis of this vulnerability through the use of endophenotypes, i.e. phenotypes that are intermediate between the genes and the more complex clinical manifestations of these diseases (Gottesman and Gould, 2003; Turetsky et al., 2007). One useful schizophrenia endophenotype may be reduced PPI of the startle reflex (Graham, 1975). Normal prepulse inhibition of startle (PPI) is a cross-species phenomenon that also occurs in humans, rats, and mice when a weak lead stimulus inhibits the response to an intense, abrupt startling stimulus. PPI is reduced in schizophrenia patients and their unaffected first-degree relatives (Braff et al., 1978, 2001; Cadenhead et al., 2000; Kumari et al., 2005) suggesting that deficient PPI may be a useful endophenotype for inherited forms of schizophrenia.

In rodents, PPI deficits can be induced by dopamine (DA) agonists such as apomorphine (APO), and recent studies have identified heritable differences in the dopaminergic regulation of PPI in both mice (Ralph and Caine, 2005) and rats (Swerdlow et al., 2004c). For example, Sprague Dawley rats from Harlan Laboratories (SD) are significantly more sensitive to the PPI-disruptive effects of dopamine (DA) agonists such as APO, compared to Long Evans rats from Harlan Laboratories (LE) (Swerdlow et al., 2001b, 2003, 2004a,b,c). These differences have been shown to be innate (Swerdlow et al., 2004a,c) and neurochemically specific (Swerdlow et al., 2003, 2004b), cannot be explained by differences in maternal behavior (Swerdlow et al., 2004a), and appear to be linked to inherited properties of DA-linked G-protein function (Swerdlow et al., 2006). Conceivably, this heritable strain difference in the "disruptability" of PPI by DA activation may provide a useful model for understanding the basis for heritable differences in PPI in disorders such as schizophrenia and Tourette Syndrome (Castellanos et al., 1996).

To date, all evidence for this SD vs. LE strain difference comes from studies in which stimuli were acoustic prepulses and

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doi:10.1016/j.pbb.2007.08.014

acoustic startle pulses. Arguably, models of heritable gating differences will be most relevant to neuropsychiatric disorders if they are not specific to one sensory modality, but rather involve integrated information across several stimulus modalities. Thus, PPI deficits in schizophrenia are evident with both uni- and cross-modal stimuli, and clinical symptoms of impaired gating involve multiple sensory modalities (Braff et al., 1992). In rats, pioneering work by Schwartz et al. (1976) demonstrated the ability to detect cross-modal PPI, using visual prepulses and acoustic pulses, and Campeau and Davis (1995) and Taylor et al. (1995) later demonstrated that APO disrupts PPI elicited by visual prepulses in SD rats. In the present study, we tested whether SD vs. LE strain differences in the gating-disruptive effects of APO occur with unimodal acoustic vs. cross-modal visual and acoustic stimulus combinations.

2. Methods

2.1. Experimental animals

Adult male SD ($n=17$) and LE ($n=17$) rats (225–250 g; Harlan Laboratories, Livermore, CA) were maintained on a reversed light/dark schedule with water and food available *ad libitum*. Rats were handled within 2 days of arrival. Testing occurred during the dark phase. All experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) and were approved by the UCSD Animal Subjects Committee (protocol #S01221).

2.2. Drugs

APO (0.01% ascorbate/saline vehicle, 0.25 or 0.5 mg/kg) was administered subcutaneously (sc) immediately prior to testing using an application volume of 1 ml/kg.

2.3. Apparatus

Startle chambers were housed in a sound-attenuated room, and consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5×25.5 cm Plexiglas frame within a ventilated enclosure. Noise bursts were presented via a speaker mounted 24 cm above the cylinder. Visual stimuli consisted of flashes of incandescent white light delivered via a 15 W light bulb. The light bulb was mounted to the ceiling of the chamber in a corner of the startle chamber at a distance of approximately 22 cm from the center of the rat cylinder. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transduced motion from within the cylinder. Stimulus delivery was controlled by the SR-LAB microcomputer and interface assembly, which also digitized (0-4095), rectified, and recorded stabilimeter readings. One hundred 1-ms readings were collected beginning at stimulus onset. Startle amplitude was defined as the average of the 100 readings.

The light stimuli were quantified using a silicon detector (stock #NT53-378, Edmund Optics, Barrington, NJ) that was soldered in parallel to a 1 kΩ resistor (RadioShack, Fort Worth, TX) and connected to an analogue oscilloscope (model #2236, Tektronix, Beaverton, OR). Changes in light intensity were displayed as voltage by the oscilloscope and recorded with a video camera (CR-HC21 NTSC, Sony, Tokyo, Japan) that was directed towards the screen of the oscilloscope. Video images were transferred to a personal computer and analyzed offline using Windows Video Maker (Microsoft, Redmond, WA). Recordings with the silicon detector were converted to approximate light intensities based on a calibration procedure during which stable light intensities were recorded in parallel on a light meter (Auto Meter IV F, Minolta Camera Co., Osaka, Japan). The 10, 20, 40 and 60 ms light flashes reached peak intensities of approximately 9, 50, 311 and 560 lx, respectively, with the tip of the silicon detector 22 cm from the light bulb. Rise times to peak for 10, 20, 40 and 60 ms light pulses were approximately 13, 22, 42 and 61 ms, respectively, and were followed by exponential decays that reached half-maximal values approximately 40, 24, 17 and 16 ms, respectively, after the peak. The light flash did not generate any audible sound as tested when the background noise and chamber ventilation were switched-off.

2.4. Startle testing procedure

Pilot experiments demonstrated insufficient PPI in response to light stimuli when startle chambers were constantly illuminated. To increase salience of the visual stimuli, all subsequent experiments were carried out with the house lights switched-off. A parametric test session was carried out in untreated animals to 1) optimize the stimulus characteristic of the visual prepulse with respect to PPI and 2) to assign rats to matched APO dose groups in the subsequent drug experiment. For the parametric experiment, rats were placed in the dark chambers for a 5 min acclimation period with a 70 dB(A) background noise. The rats were then exposed to a series of trial types which were presented in pseudorandom order: (1) 40 ms — 120 dB(A) noise burst (P-ALONE); (2) P-ALONE preceded 100 ms (onset-to-onset) by a 20 ms noise burst 10 dB above background (PP10dB+P-ALONE); (3–6) P-ALONE preceded 100 ms (onset-to-onset) by a light flash of either 10 ms (LI10ms+P-ALONE), 20 ms (LI20ms+P-ALONE), 40 ms (LI40ms+P-ALONE) or 60 ms (LI60ms+P-ALONE) duration; (7) a 20 ms noise burst 10 dB above background (PP10dB-ALONE); (8) a 60 ms light flash (LI60ms-ALONE). Interspersed between any of these trial types was a trial in which no stimulus was presented, but motor activity was measured (NOSTIM trials). Not taking NOSTIM trials into account, the session began with 3 consecutive P-ALONE trials and ended with 3 consecutive P-ALONE trials; between these trials was one block consisting of 8 trails of each of the other 8 active stimulus types. Intertrial intervals were variable and averaged 15 s. NOSTIM trials were not included in the calculation of inter-trial intervals. Total session duration was 22.5 min.

Based on the parametric test session, a duration of 40 ms was selected for the light flash in the drug experiment. Rats were assigned to APO dose groups (0, 0.25, 0.5 mg/kg) based on average %PPI derived from responses to acoustic (PP10dB+P-ALONE) and visual (40 ms; LI40ms+P-ALONE) prepulse trails of the test session.

Drug testing began 1 day after the parametric test session for a total of 3 test days in a within subject, pseudorandom balanced dose order design, with 3 days between tests. After the injection

of vehicle or APO, rats were immediately placed in the dark startle chambers for a 5 min acclimation period with a 70 dB(A) background noise. The rats were then exposed to a series of trial types presented in pseudorandom order: (1) P-ALONE; (2) PP10dB+P-ALONE; (3) LI40ms+P-ALONE; (4) PP10dB-ALONE; and (5) a 40 ms light flash (LI40ms-ALONE). Interspersed between any of these trial types was a NOSTIM trial. Not taking NOSTIM trials into account the session began with 3 consecutive P-ALONE trials and ended with 3 consecutive P-ALONE trials; between these trials were two blocks, each consisting of 6 P-ALONE, 6 LI40ms+P-ALONE, 6 PP10dB+P-ALONE, 3 LI40ms-ALONE and 3 PP10dB-ALONE trails. Intertrial intervals were variable and averaged 15 s. NOSTIM trials were not included in the calculation of inter-trial intervals. Total session duration was 18.5 min.

2.5. Data analysis

PPI was defined as 100−[(startle amplitude on prepulse trials/startle amplitude on P-ALONE trials)×100], and was analyzed by mixed design ANOVAs. The values for the acoustic startle P-ALONE were used in separate calculations of both unimodal (acoustic prepulse+P-ALONE stimuli) and cross-modal (light prepulse+acoustic P-ALONE stimuli) PPI. Other ANOVAs were used to assess P-ALONE magnitude, as well as activity recorded in the aftermath of prepulses alone, or NOSTIM trials. Post-hoc comparisons were conducted using Fisher's PLSD. Alpha was 0.05.

3. Results

3.1. Light prepulse duration and cross-modal PPI

Separate ANOVAs of PPI were carried out for the two prepulse modalities. No strain effects on PPI were detected in response to acoustic prepulses ($F=2.30$, df 1,32, ns). The ANOVA of PPI for visual prepulses revealed a significant main effect of strain (SD>LE, $F=12.39$, df 1,32, $p<0.002$) and light duration ($F=42.05$, df 3, 96, $p<0.0001$), but no strain×light duration interaction ($F<1$, df 3,96, ns; Fig. 1). Post-hoc analyses revealed that %PPI exhibited an "inverted-U" function: highest values for the 40 ms light flash, lowest for the 10 ms light flash, and intermediate values for the 60 ms and 20 ms light flash (40 ms>60 ms>20 ms>10 ms, $p<0.005$ for all comparisons). Acoustic startle magnitude did not differ between strains ($F<1$, df 1,32, ns; Fig. 1, inset).

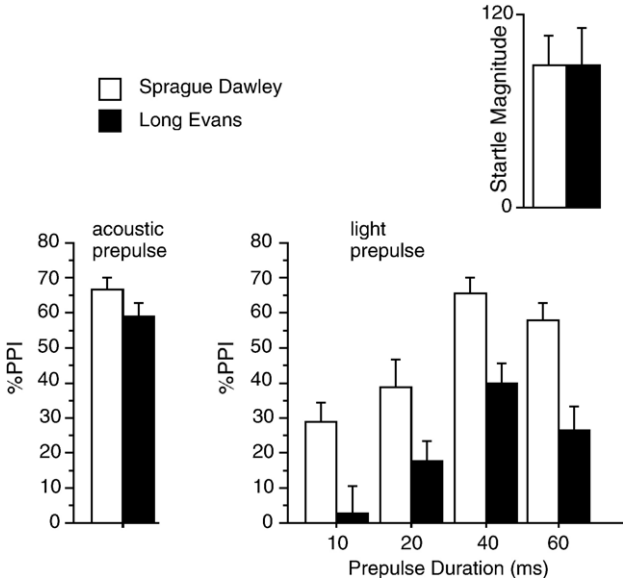

Fig. 1. %PPI and startle magnitude (inset) in response to either an acoustic prepulse (10 dB above background) or a visual prepulse of either 10, 20, 40 or 60 ms duration in SD rats (open bars) and LE rats (solid bars). Startle magnitude was similar in SD and LE rats (ns). Both rat strains had similar %PPI in response to acoustic prepulses (ns). For both strains %PPI to visual prepulses was strongly depended on prepulse duration ($p<0.0001$). PPI was lowest at a prepulse duration of 10 ms and reached peak values at 40 ms. SD rats exhibited more PPI to visual prepulses than did LE rats ($p<0.002$).

3.2. APO effects on uni- and cross-modal PPI

ANOVA of %PPI revealed significant main effects of strain ($F=6.14$, df 1,32, $p<0.02$) and APO dose ($F=22.81$, df 2,64, $p<0.0001$), and a significant strain×dose interaction ($F=12.38$, df 2,64, $p<0.0001$). There was a significant effect of prepulse modality (acoustic>light; $F=5.36$, df 1,32, $p<0.03$), and a significant interaction of APO dose×modality ($F=3.88$, df 2,64, $p<0.03$), but no significant interaction of dose×modality×strain ($F=2.80$, df 1,32, ns). Separate ANOVAs for each prepulse modality revealed significant interactions of strain×dose (acoustic: $F=9.52$, df 2,64, $p<0.0002$; visual: $F=9.26$, df 2,64, $p<0.0003$), in each case reflecting greater sensitivity to the PPI-disruptive effects of APO in SD rats (Fig. 2). Post-hoc comparisons revealed significant PPI-disruptive effects of APO in SD rats with both acoustic ($F=19.73$, df 2,32, $p<0.0001$) and visual prepulses ($F=10.62$, df 2,32, $p<0.0004$). For LE rats, APO significantly reduced PPI with acoustic prepulses ($F=5.04$, df 2,32, $p<0.015$), but not with visual prepulses ($F=1.87$, df 2,32, ns).

ANOVA of startle magnitude on P-ALONE trials revealed significant main effects of strain (LE>SD; $F=7.99$, df 1,32, $p<0.009$) and APO dose ($F=14.19$, df 2,64, $p<0.0001$), and a significant strain×dose interaction ($F=4.86$, df 2,64, $p<0.015$). This interaction reflected significant startle-enhancing effects of APO in LE rats ($F=13.68$, df 2,32, $p<0.0001$), but not in SD rats ($F=2.18$, df 2,32, ns).

To assess the impact of APO effects on startle on PPI differences, a separate analysis was carried out for subsets of rats constructed by eliminating the extreme responders until the effects of apomorphine on startle magnitude were numerically balanced across strains (mean (SEM) of startle magnitude in these subsets of rats: SD: vehicle=122 (26), APO 0.25 mg/kg=113 (23), APO 0.5 mg/kg=122 (20), $n=5$; LE: vehicle=136 (46), APO 0.25 mg/kg=126 (20), APO 0.5 mg/kg=160 (26), $n=5$). ANOVA of startle magnitude on P-ALONE trials in these rats confirmed a lack of effect of strain ($F<1$, df 1,8, ns), APO dose ($F<1$, df 2,16, ns), and strain×dose ($F<1$, df 2,16, ns). ANOVA of %PPI in these subgroups confirmed the key results: a

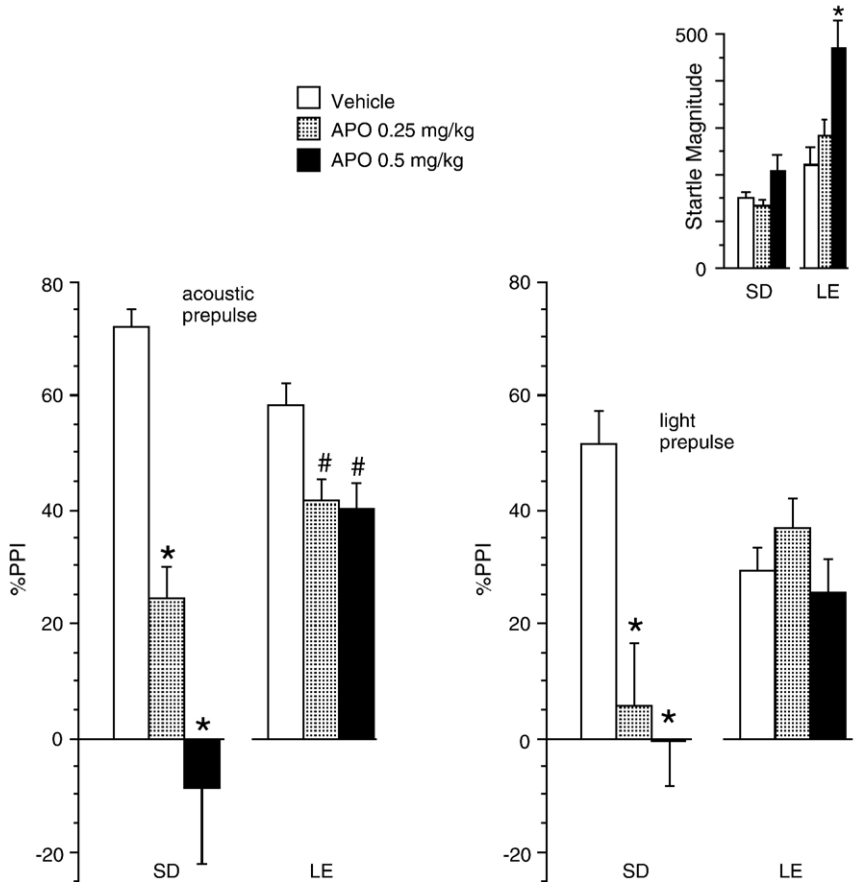

Fig. 2. Effects of APO on %PPI and startle magnitude (inset) in response to acoustic vs. visual prepulses in SD and LE rats. ANOVA revealed a significant main effect for strain, APO dose, and prepulse modality ($p<0.02$, $p<0.0001$, and $p<0.03$ respectively) and significant interactions for APO dose × prepulse modality and strain × APO dose ($p<0.03$ and $p<0.0001$, respectively), with greater APO sensitivity on PPI for SD than LE rats. PPI APO sensitivity was greater for SD vs. LE rats with prepulses from both acoustic ($p<0.0002$) and visual modalites ($p<0.0003$). Fisher's PLSD post-hoc tests revealed that APO reduced acoustic PPI in SD rats (*$p<0.0005$ for 0.25 and 0.5 mg/kg doses vs. vehicle) and in LE rats ($^{\#}p<0.02$ for 0.25 and 0.5 mg/kg vs. vehicle). Visual PPI was reduced by APO in SD rats (*$p<0.0005$ for 0.25 and 0.5 mg/kg doses vs. vehicle), but not in LE rats (ns). Startle response magnitude was increased by APO at the highest dose in LE rats (*$p<0.0005$ for 0.5 mg/kg dose vs. vehicle), but not in SD rats (ns).

significant main effect of APO dose ($F=10.42$, df 2,16, $p<0.002$) and a significant strain × dose interaction ($F=5.57$, df 2,16, $p<0.02$). No significant effects of strain, prepulse modality, APO dose × modality, and dose × modality × strain were detected. Separate ANOVAs for each strain revealed significant effects of APO dose in SD rats ($F=14.86$, df 2,8, $p<0.005$), but not in LE rats ($F<1$, df 2,8, ns) confirming greater APO PPI sensitivity in SD rats than LE rats with both uni- and cross-modal stimuli, independent of APO effects on startle. Simple regression analyses provided confirmatory information, revealing no significant correlations of APO effects on startle magnitude vs. PPI, for any APO dose or prepulse modality within either SD or LE strains.

Inspection of motor activity (cage displacement) on prepulse alone trials in vehicle-treated rats revealed small signals that differed across stimulus modalities. ANOVA of prepulse-induced motor activity revealed no significant effects of strain or APO dose, and no significant interactions of dose × strain, or dose × strain × modality (all comparisons ns). Much of this motor "signal" reflected ongoing, rather than stimulus-triggered, movement: subtraction of NOSTIM activity from activity measured in the aftermath of light prepulses yielded values indistinguishable from zero units for both SD and LE rats. Separate analysis of NOSTIM levels revealed significant effects of APO that were more robust in SD than LE rats. However, neither correlational analyses nor ANCOVAs revealed any consistent relationship between differential APO effects on PPI and motor activity across strains.

4. Discussion

We previously reported greater sensitivity of SD than LE rats to the PPI-disruptive effects of systemically administered DAergic agonists, including APO, D-amphetamine and quinpirole (Swerdlow et al., 2001b, 2003, 2004a,b,c). These studies demonstrated the effects of dopamine agonists on PPI under conditions in which both prepulse and pulse were acoustic stimuli. These effects on acoustic PPI were replicated in the present study. The APO-disruption of visual PPI in SD rats reported here also confirm findings from an earlier report by Campeau and Davis (1995). Importantly, in the present study, we demonstrated for the first time that heritable strain differences in

the gating-disruptive effects of APO extend to cross-modal PPI, i.e. PPI elicited by a visual prepulse and an acoustic pulse.

Conceivably, relatively reduced PPI in LE rats after vehicle treatment might contribute to the blunted impact of APO on acoustic and visual PPI, via a "floor effect". However, a floor effect cannot explain the present findings, because in both modalities, PPI after APO treatment was substantially *greater* in LE than SD rats. Differential motor responses to prepulses might also conceivably contribute to SD vs. LE difference in PPI APO sensitivity, but the present data also do not support such an interpretation: analyses of motor activity after prepulses revealed that both strain × APO dose ($p=0.28$) and strain × APO dose × modality ($p=0.76$) interactions failed to reach statistical significance despite substantial power afforded by the current sample sizes ($n=17$ per strain). Finally, strain-specific APO effects on startle magnitude cannot account for the observed strain differences in APO sensitivity for acoustic and visual PPI, because these PPI differences were evident even among "matched" subsets of SD and LE rats that exhibited comparable APO effects on startle.

The present findings have several implications. First, they provide another level of homology between the clinical data of uni- and cross-modal gating deficits in several different brain disorders, and an animal model of heritable differences in uni- and cross-modal PPI "disruptability". Thus, PPI deficits in schizophrenia patients are detected with both acoustic prepulses and pulses, and with acoustic prepulses and tactile (air puff) pulses (Braff et al., 1992). Similarly, PPI deficits in Tourette Syndrome are evident with either acoustic or tactile stimuli, the latter including both facial shocks (Castellanos et al., 1996) and air puffs (Swerdlow et al., 2001a). Thus, at least in these two heritable brain disorders, gating deficits are not modality-specific.

Second, the present findings provide a basis for strong inference regarding the anatomical substrates responsible for these heritable gating differences. Thus, the simplest explanation for the strain-specific APO effects on both acoustic and cross-modal PPI is that these effects are mediated by circuitry that processes integrated information, at a level beyond the convergence of separate auditory and visual sensory streams. Such circuitry also regulates PPI, and exhibits strain differences in the effects of DA receptor stimulation on cellular events. We have hypothesized that the nucleus accumbens (NAC) may be one critical substrate contributing to these heritable differences in PPI APO sensitivity, based in part on evidence that LE and SD rats differ significantly in the effects of APO on NAC measures of activity within DA-linked signal transduction pathways, including DA-stimulated GTPγS binding (Swerdlow et al., 2006), phosphorylation of cyclic AMP binding protein (CREB) in the NAC (Saint Marie et al., 2007) and NAC FOS activation (Saint Marie et al., 2006), and that these strains also differ significantly in their characteristic gene activation patterns within NAC signal pathways (Shilling et al., 2007). If the present study had revealed that SD vs. LE differences in PPI APO sensitivity were limited to unimodal acoustic stimuli, it would be very difficult to argue that cellular mechanisms in the NAC mediate the heritable differences in gating phenotypes in this animal model, and by extension, in schizophrenia or other complex brain disorders.

Rat strain differences in drug sensitivity might reflect genetic or epigenetic influences on a number of different biological systems, and many such differences undoubtedly arise from mechanisms with little relevance to the genesis of neuropsychiatric disorders. The specific strain differences described in these studies have been pursued experimentally from the "top-down", i.e. from the levels of possible fostering effects and maternal–pup interactions, to different parametric behavioral manipulations, through possible pharmacodynamic mediators, neurochemical and neuroanatomical substrates, and more recently to regionally specific signal transduction mechanisms and gene expression. Both the neurobiological mechanisms under investigation (genetic control of NAC DA-linked signal transduction) and the phenotype (low vs. high DA-mediated PPI "disruptability") are ones that could be reasonably viewed as being of potential relevance to human brain disorders. Conceivably, within the molecular pathways controlling these mechanisms and phenotypes will be targets for therapeutic interventions in heritable disorders of impaired PPI, such as schizophrenia and Tourette Syndrome.

This study was not designed to provide a full parametric mapping of stimulus–response characteristics for cross-modal PPI in SD and LE rats. Nonetheless, we note that, compared to albino SD rats, pigmented LE rats exhibited less PPI in response to visual prepulses for all prepulse durations. This observation is consistent with reports of greater sensitivity to photic stimulation within the superior colliculus in albino vs. pigmented rats (Thomas et al., 2005).

In summary, heritable differences in the sensitivity to the gating-disruptive effects of DA stimulation in SD and LE rats occur when gating is produced with either uni- or cross-modal stimulus pairs. The simplest explanation for the present findings is that these SD vs. LE differences are mediated by circuitry outside the auditory system, within forebrain circuitry that integrates information streams across multiple sensory modalities. The present findings provide further validation for this heritable model of impaired sensorimotor gating in schizophrenia, which is also detected across multiple sensory modalities.

Acknowledgements

Research supported by MH01436 and MH68366. The authors gratefully acknowledge the assistance of Maria Bongiovanni in manuscript preparation, Dr. Martin Vogel and Richard F. Sharp for technical expertise and David Ko for critical discussion.

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