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Heritable differences in the effects of amphetamine but not DOI on startle gating in albino and hooded outbred rat strains

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Abstract

Sensorimotor gating, measured by prepulse inhibition (PPI) of the startle reflex, is reduced in schizophrenia patients and in rats treated with dopamine (DA) agonists. Strain and substrain differences in the sensitivity to the PPI-disruptive effects of DA agonists may provide insight into the basis for human population differences in sensorimotor gating. We reported heritable differences in sensitivity to the PPI-disruptive effects of the D1/D2 agonist apomorphine (APO) in Harlan Sprague–Dawley (SDH) and Long–Evans (LEH) rats, offspring (F1) of an SDH × LEH cross, and subsequent offspring (N2) of an SDH × F1 cross. In this study, we assessed the neurochemical specificity of this heritable phenotype across parental SDH and LEH strains, and their F1 and N2 offspring, based on their sensitivity to the PPI-disruptive effects of the indirect DA agonist D-amphetamine (AMPH) and the 5HT2A agonist DOI. AMPH sensitivity followed a gradient of SDH>N2>F1>LEH, consistent with past findings with APO. DOI sensitivity did not differ across strains or generations. These findings demonstrate that the heritable phenotype in this model is not specific to a particular compound (APO), and reflects physiological differences in the DAergic, but not serotonergic, regulation of PPI.

Keywords: Amphetamine; Apomorphine; DOI; Dopamine; Prepulse inhibition; Schizophrenia; Serotonin; Startle; Strain

1. Introduction

The startle response to an intense, abrupt stimulus is normally inhibited when a weak prepulse precedes the startling stimulus by 30–500 ms. The degree to which startle is inhibited by the prepulse is an operational measure of sensorimotor gating (Graham, 1975). Prepulse inhibition (PPI) is deficient in certain neuropsychiatric disorders, and may be a useful endophenotype for understanding the genetic basis for these disorders. For example, PPI is significantly reduced in schizophrenia probands and first-degree relatives, compared with unaffected controls without a familial history of schizophrenia (Braff et al., 1978; Cadenhead et al., 2000). Both human and infrahuman studies suggest that PPI is regulated by limbic cortical and ventral striatal circuitry that is relevant to the pathophysiology of schizophrenia (cf., Koch and Schnitzler, 1997; Swerdlow and Geyer, 1998; Swerdlow et al., 2001a). By understanding the genetic and neural regulation of PPI, it might be possible to test hypotheses related to the more complex phenotype of schizophrenia.

In rats, PPI is reduced by dopamine (DA) agonists such as the mixed D1/D2 agonist apomorphine (APO) (Swerdlow et al., 1986; cf., Geyer et al., 2001; Mansbach et al., 1988), and the ability of drugs to restore PPI in APO-treated rats strongly predicts antipsychotic potency (Swerdlow et al., 1994). Strain differences in PPI APO sensitivity were first reported by Rigdon (1990), and have since been identified in several outbred rat populations (Hitchcock et al., 1999; Swerdlow et al., 1997, 2000, 2001c, 2003a,b,c; Kinney et al., 1999). For example, we reported that albino Harlan Sprague–Dawley (SDH) rats are more sensitive than hooded Harlan Long–Evans (LEH) rats to the PPI-disruptive effects of APO. These strain differences are stable across breeding facilities (Swerdlow et al., 2001c), are evident early in development (on or before Day 18), cannot be explained on the basis of differential absorption or CNS concentration of APO (Swerdlow et al., 2002), and are inherited with a pattern that suggests simple additive effects

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of multiple genes (Swerdlow et al., 2003b,c). PPI APO sensitivity follows an orderly gradient across generations (SDH>N2>F1>LEH), reflecting the fact that a larger dose of SDH genes conveys greater APO sensitivity. SDH>LEH sensitivity is unaltered by cross-fostering, suggesting that nongenomic influences do not play a major role in this phenotype (Swerdlow et al., 2003c).

This strain difference may provide insight into the neural basis of an inherited vulnerability for a DA-mediated loss of sensorimotor gating, which might be relevant to the loss of PPI associated with inherited perturbations of DA function commonly seen in outbred human populations (e.g., schizophrenia and Tourette syndrome) (cf., Braff et al., 2001). However, the utility of this model hinges to some degree on its neurochemical specificity. Thus, this model might turn out to be relatively uninteresting if it (1) reflects some property that is unique to APO, or (2) reflects a generalized disruptability of PPI to all neurochemical manipulations. This issue was addressed in the present studies by examining the sensitivity of SDH, LEH, F1, and N2 rats to the PPI-disruptive effects of the indirect DA agonist D-amphetamine (AMPH), and to the 5HT2A agonist DOI. If this heritable phenotype reflects processes that are specific to APO, then it should not be evident with *either* AMPH or DOI. Alternatively, if this heritable phenotype reflects a "generalized disruptability" in PPI, it should be observed with *both* AMPH and DOI. Finally, if this heritable phenotype reflects a physiological difference that is neurochemically specific to DA function, then it should be *evident with AMPH, but not DOI.*

2. Materials and methods

2.1. Experimental animals

A total of 298 adult male and female rats were used in these experiments. SDH and LEH rats were obtained as adults from commercial suppliers [SDH: Harlan Laboratories, San Diego, CA (facility no. 235); LEH: Harlan Laboratories, Madison, WI (facility no. 207)]; these were also the sources of rats for the parental F0 generation. F1 (SDH × LEH) rats and N2 (SDH × F1) rats were bred as described below; most rats had been tested in measures of PPI on at least one occasion as pups or adults, as reported elsewhere (Swerdlow et al., 2003b,c). Because of the significant resource investment in breeding these rats, they were allowed to mature to adulthood, and were then utilized in the present studies.

Methods for housing and all behavioral testing were consistent with the substantial literature of startle measures in rodents (cf., Geyer and Swerdlow, 1998). Briefly, timed pregnant female LEH and SDH rats were housed individually, and litters were sorted as described below. Aside from the strain of the nursing female rat, rearing conditions for all pups were comparable; parental strains, F1, and N2 generations were raised in the same rooms, on the same cage racks. Adult male and nonpregnant female rats were each housed in same-sex rooms (except for rats used for breeding), in groups of two to four. After shipment arrival, rats obtained from commercial vendors were maintained in the housing facility on a reversed 12-h light/dark cycle (lights on at 1900 h, off at 0700 h) for at least 1 week prior to behavioral testing. All testing and drug administration occurred between 0900 and 1700 h. Rats were handled regularly prior to any procedures to minimize stress during behavioral testing, and were given ad libitum access to food and water except during behavioral testing. Throughout these studies, all efforts were made to minimize animal suffering and to reduce the number of animals used. All experiments conform to guidelines of the National Research Council for the use of animals in biomedical research and were approved by the Animal Subjects Committee at the University of California, San Diego (protocol nos. 0224909 and SO1221).

2.2. Drugs

AMPH (saline vehicle, 1.5, 3.0, or 4.5 mg/kg sc) was administered subcutaneously to rats 10 min prior to testing. The 4.5-mg/kg dose of AMPH yields a consistent reduction in PPI in SDH rats, based on our past experience (Mansbach et al., 1988). DOI [1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane] (saline vehicle, 0.25, 0.5, or 1.0 mg/kg sc) was administered subcutaneously to rats 10 min prior to testing. The 1.0-mg/kg dose of DOI yields a consistent reduction in PPI in SDH rats, based on our past experience (Farid et al., 2000).

2.3. Apparatus

Startle experiments used four startle chambers (SR-LAB; San Diego Instruments, San Diego, CA) housed in a sound-attenuated room with a 60-dB ambient noise level. Each startle chamber consisted of a Plexiglas cylinder (8.7 cm, internal diameter) resting on a 12.5 × 25.5-cm Plexiglas stand. Acoustic stimuli and background noise were presented via a Radioshack Supertweeter mounted 24 cm above the Plexiglas cylinder. Startle magnitude was detected and recorded as transduced cylinder movement via a piezoelectric device mounted below the Plexiglas stand. Response sensitivities were calibrated (SR-LAB Startle Calibration System) to be nearly identical in each of the four startle chambers (maximum variability $<1\%$ of stimulus range and $<5\%$ of response ranges). Chambers were also balanced across all experimental groups. Sound levels were measured and calibrated with a sound level meter (Quest Electronics, Oconomowoc, WI), A scale (relative to 20 μN/M2), with microphone placed inside the Plexiglas cylinder. Methodological details can be found in published material (Geyer and Swerdlow, 1998).

2.4. Startle testing procedures

To assign dose groups, rats were exposed to a brief "matching" startle session 2–4 days prior to first testing, as reported previously (Geyer and Swerdlow, 1998). Rats were placed in a startle chamber, and exposed to 5 min of 70-dB background noise followed by 17 "PULSE" trials of 40-ms, 120-dB noise bursts and three "PREPULSE" trials consisting of a 20-ms, 82-dB (12 dB above background) prepulse followed by 100-ms, 120-dB pulse (onset to onset). Data from this session were used to assign rats to balanced dose groups.

Rats were brought to the laboratory in their home cages, weighed, and placed in individual cages. Test sessions were approximately 19 min long and consisted of 5 min of 70 dB background followed by five trial types: PULSE noise bursts, PREPULSE trials (20-ms noise bursts 5, 10, or 15 dB above background followed after 100 ms by a PULSE) and NOSTIM trials (stabilimeter recordings obtained when no stimulus was presented). The session consisted of initial and final blocks of three PULSE trials, separated by two blocks that included 8 PULSE trials and 15 PREPULSE trials (the latter divided equally among 5-, 10-, and 15-dB prepulse intensities); "NOSTIM" trials were interspersed between startle trials. NOSTIM trials were used to assess gross motor activity during the test session, but were not included in the calculation of intertrial intervals, which were variable and averaged 15 s. Reflex "habituation" was determined based on the change in startle magnitude from the initial to the final block of PULSE trials. Using this design, PPI is measured during a portion of the session in which startle magnitude is relatively constant (i.e., has already undergone the maximal rate of habituation during the initial three PULSE trials).

Rats ($n = 224$) were tested first with DOI (vehicle, 0.25, 0.5, or 1.0 mg/kg sc). One week later, tests were conducted with AMPH (vehicle, 1.5, 3.0, or 4.5 mg/kg sc); of the rats in the AMPH study ($n = 179$), more than half ($n = 105$) had previously been tested with DOI, and the remaining rats ($n = 74$) were drug-naive.

2.5. Breeding procedures and drug histories

To produce an F1 population, SDH and LEH rats were reciprocally crossed (with equal representation of both sexes from both strains). SDH and LEH rats were naive to drug and testing, and only males were used for testing. F1 (SDH × LEH) litters were allowed to mature to adulthood, without testing as pups. Approximately half of the SDH × F1 ("N2") rats were tested with APO as pups, and then allowed to mature to adulthood, while the other N2 rats remained drug-naive until their adult tests. Because of the various different drug histories in F1 and N2 rats prior to their adult testing with DOI and AMPH in the present study, drug sensitivity was examined as a function of these drug histories. ANOVAs revealed no interactions between drug sensitivity and either history of testing as pups or history of testing as adults.

2.6. Data analysis

PPI was calculated as a percent reduction in startle magnitude on PREPULSE trials compared to PULSE trials. Any drug effects on %PPI prompted separate analyses to assess the relationship of these effects to drug-induced changes in startle magnitude on PULSE and PREPULSE trials. All startle data were analyzed using an ANOVA with Strain, Drug Treatment, and Sex (for F1 and N2) as between-subject factors and Trial Block and Trial Type as within-subject repeated measures. Relevant ANOVA values are shown in Table 1. Because comparisons revealed no informative statistically significant interactions with prepulse intensity, trial block, or sex, data were collapsed across these variables for presentation purposes. A measure of drug "effect" [mean PPI after vehicle minus mean PPI

Table 1
Statistical summary

Drug	Variable	Factor	*F*	*df*	Significance (*P*)
DOI	Percent PPI	Strain	2.27	3,208	ns
		Dose *	8.95	3,208	< .0001
		Strain × Dose	< 1		
	"DOI effect"	Strain	< 1		
		Dose	2.13	2,161	ns
		Strain × Dose	< 1		
	Startle magnitude	Strain	6.20	3,208	< .001
		Dose	1.01	3,208	ns
		Strain × Dose	< 1		
	NOSTIM level	Strain	3.33	3,208	< .025
		Dose * *	3.82	3,208	< .02
		Strain × Dose	1.30	9,208	ns
AMPH	Percent PPI	Strain	4.67	3,117	< .005
		Dose* * *	4.67	3,117	< .005
		Strain × Dose	1.61	9,117	ns
	"AMPH effect"	Strain* * * *	5.62	3,88	< .002
		Dose	3.56	2,88	< .04
		Strain × Dose	1.44	6,88	ns
	Startle magnitude	Strain	4.43	3,117	< .006
		Dose	2.11	3,117	ns
		Strain × Dose	1.12	9,117	ns
	NOSTIM level	Strain	1.62	3,117	ns
		Dose	< 1		
		Strain × Dose	< 1		

* Vehicle vs. 0.25, 0.5, 1.0 mg/kg: $P < .0001$ all doses.

** Vehicle vs. 1.0 mg/kg: $P < .007$.

*** SDH: vehicle vs. 3.0 and 4.5 mg/kg: $P < .007$ and $P = .001$, respectively; N2: vehicle vs. 3.0 mg/kg: $P < .02$.

**** SDH vs. LEH: $P < .005$; SDH vs. F1: $P < .001$; SDH vs. N2: $P < .053$; N2 vs. LEH: $P < .053$; N2 vs. F1: $P < .025$.

after active (nonvehicle) drug dose] was also calculated and compared across strains; this value has previously been shown to be very sensitive to differences across strains and generations, in studies with APO (Swerdlow et al., 2003a,c). Post-hoc comparisons of significant interaction effects and relevant main factor effects were conducted using Fisher's protected least significant difference (PLSD) and one-factor ANOVA tests. Initial analyses of strain differences in sensitivity to the PPI-disruptive effects of DOI and AMPH included all four strains (SDH, LEH, F1, and N2) and four doses of each drug. However, based on our past findings (Swerdlow et al., 2003a,c), specific comparisons with F1 and N2 strains were planned a priori, with the following simple "additive" model predictions: (1) SDH and LEH sensitivity would differ by the largest magnitude; (2) F1 sensitivity would be intermediate between parental strains; and (3) N2 sensitivity would be intermediate between F1 and SDH. The α value was .05.

For ease of presentation, unless otherwise stated, several normal parametric effects can be assumed to be statistically significant in all startle analyses: effects of trial block on startle magnitude, and effect of prepulse intensity on PPI. For most instances, only statistically significant effects, or those relevant to the critical comparisons, are reported in detail.

3. Results

The major dependent measure of these studies was PPI. All findings with this measure, in addition to startle magnitude, are summarized in the text and in Tables 1 and 2. Additional behavioral measures are also reported because they may influence the interpretation of PPI results.

DOI significantly reduced PPI, and no difference was observed in DOI sensitivity across the four strains. ANOVA revealed a significant effect of DOI Dose ($P<.0001$), but no significant effects of Strain or Dose × Strain interaction (Fig. 1A). Inspection of the data revealed similar dose-dependent reductions in PPI across all strains. Post-hoc comparisons revealed significant reductions in PPI after the 0.25-, 0.5-, and 1.0-mg/kg doses ($P<.0001$, all doses). Among N2 rats, no difference in DOI sensitivity was observed between those with albino vs. hooded phenotypes. Calculation of the magnitude of the "DOI effect" (amount by which DOI reduced PPI, compared to vehicle levels for each strain) revealed no differences across generations ($F<1$).

AMPH significantly reduced PPI in SDH and N2 rats, but not in LEH or F1 rats. ANOVA revealed significant effects of AMPH Dose ($P<.005$) and Strain ($P<.005$), but the Strain × Dose interaction did not reach significance. Planned comparisons confirmed that this interaction reached significance when only the parental strains (SDH and LEH) were included ($P<.02$), and that AMPH significantly reduced PPI in SDH rats (at 3.0- and 4.5-mg/kg doses: $P<.007$ and $P<.001$, respectively), and in N2 rats (at the 3.0-mg/kg dose, $P<.02$), but not in either LEH or F1 rats (Fig. 1B). Among N2 rats, no difference in AMPH sensitivity was observed between those with albino vs. hooded phenotypes.

Calculation of the "AMPH effect" (amount by which AMPH reduced PPI, compared to vehicle levels for each strain) revealed a significant effect of Strain ($P<.002$) and AMPH Dose ($P<.04$), but no significant interaction (Fig. 1B, inset). Again, planned comparisons revealed that the AMPH effect was significantly greater in SDH rats than in LEH ($P<.005$) or F1 rats ($P<.001$), and was significantly

Table 2
Startle values [mean (S.E.M.)]

Variable	Drug	Dose (mg/kg)	Strain			
			SDH	N2	F1	LEH
Startle magnitude	DOI	Vehicle	236.80 (26.33)	244.13 (24.93)	269.60 (28.89)	395.53 (79.77)
		0.25	319.02 (34.99)	254.47 (25.59)	283.29 (31.17)	519.63 (126.46)
		0.5	280.83 (43.29)	263.414 (22.64)	273.31 (24.89)	310.64 (57.64)
		1.0	234.93 (29.97)	218.19 (18.99)	261.47 (17.33)	441.96 (67.02)
NOSTIM level		Vehicle	0.00 (0.00)	0.10 (0.05)	0.03 (0.01)	0.14 (0.09)
		0.25	0.23 (0.11)	0.19 (0.05)	0.57 (0.20)	2.08 (1.39)
		0.5	0.76 (0.33)	0.72 (0.18)	0.80 (0.60)	1.13 (0.37)
		1.0 *	0.99 (0.44)	0.58 (0.10)	0.75 (0.16)	4.60 (3.34)
Startle magnitude	AMPH	Vehicle	292.56 (16.46)	289.01 (37.70)	569.84 (106.89)	315.33 (82.33)
		1.5	199.34 (56.87)	155.47 (18.92)	370.45 (35.42)	377.19 (86.88)
		3.0	473.83 (58.05)**	280.85 (35.57)	445.93 (50.54)	562.83 (199.32)
		4.5	585.70 (48.75)***	383.87 (88.52)	475.89 (38.88)	266.60 (45.97)
NOSTIM level		Vehicle	0.10 (0.06)	0.19 (0.15)	0.09 (0.05)	0.33 (0.13)
		1.5	0.00 (0.00)	0.22 (0.11)	0.12 (0.05)	0.44 (0.13)
		3.0	0.43 (0.22)	0.66 (0.33)	0.13 (0.07)	0.01 (0.01)
		4.5	0.21 (0.07)	0.23 (0.07)	0.13 (0.05)	0.07 (0.05)

* Significant increase vs. vehicle, $P<.007$.
** Significant increase vs. vehicle, $P<.04$.
*** Significant increase vs. vehicle, $P<.003$.

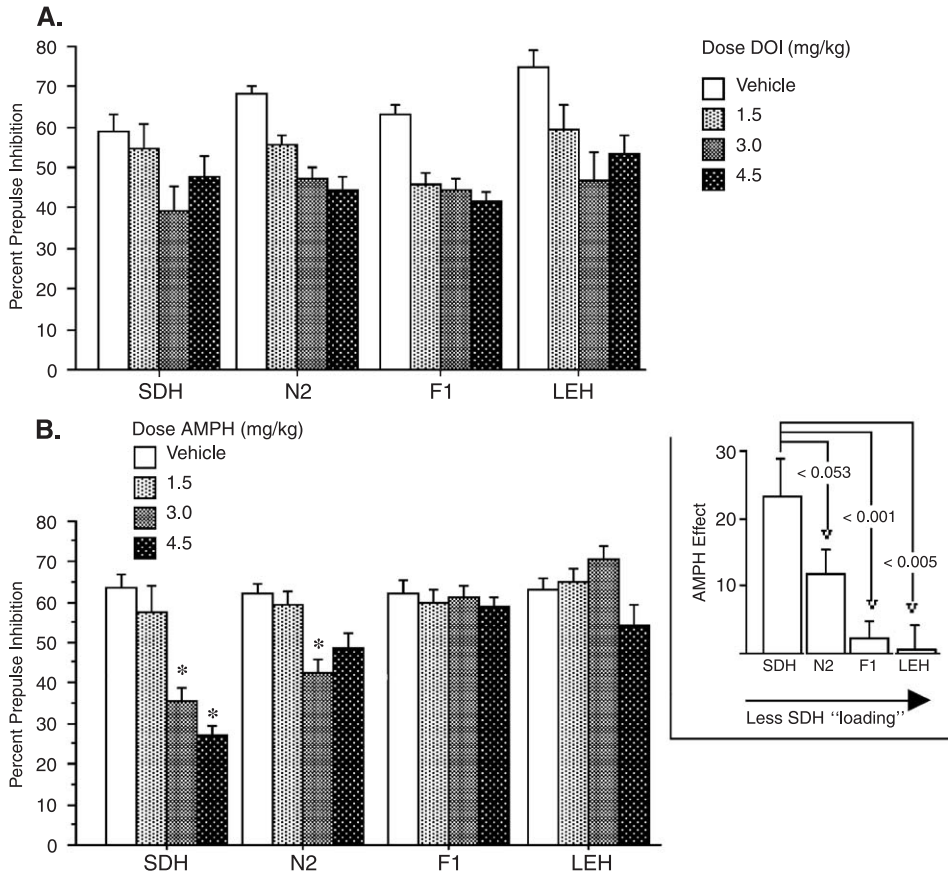

Fig. 1. Effects of DOI (A) and AMPH (B) on PPI in SDH, N2, F1, and LEH rats. (A) DOI reduced PPI across all rat strains (main effect of Dose, $P < .0001$), but there were no differences in DOI sensitivity across strains. Group sizes (n): SDH = 17, LEH = 18, F1 = 91, and N2 = 98. (B) AMPH reduced PPI in SDH and N2 rats, but not in F1 or LEH rats. Group sizes (n): SDH = 17, LEH = 17, F1 = 92, and N2 = 53. * Significant effects of AMPH dose on PPI ($P < .007$ and $P = .001$ for 3.0 and 4.5 mg/kg doses in SDH rats, and $P < .02$ for 3.0 mg/kg dose in N2 rats). Inset: AMPH effect on PPI (amount by which AMPH reduced PPI, compared to vehicle levels for each strain), collapsed across AMPH doses, follows the predicted linear trend, based on a declining "loading" of SDH genes, progressing from SDH to N2 to F1 to LEH rats. Significance levels vs. SDH rats are shown in the figure; other contrasts included N2 vs. F1 ($P < .025$) and N2 vs. LEH ($P < .053$).

greater in N2 rats compared to F1 ($P < .025$) rats; contrasts of N2 vs. SDH and LEH rats both approached significance ($P < .053$, both comparisons). Thus, the overall pattern of AMPH sensitivity followed the predicted generational gradient: SDH>N2>F1>LEH (Fig. 1B). This trend exhibited significant linear ($t = 3.75$, $P < .0005$), but not quadratic ($t = 1.15$, ns), changes. Among N2 rats, no difference in AMPH sensitivity was observed between those with albino vs. hooded phenotypes.

There were no significant main effects of DOI or AMPH on startle magnitude, nor significant Dose × Strain interactions (Table 1). Significant strain differences in startle magnitude were noted, but the pattern of strain differences was inconsistent across studies. Analyses in the DOI study revealed no strain differences at the vehicle dose, but elevated startle magnitude in LEH rats compared to other strains at most active doses; no significant effects of DOI were noted within any single strain. In contrast, analyses in the AMPH study revealed lower startle magnitude in N2 vs. F1 rats at the vehicle dose, and significant increases in startle magnitude in SDH rats with the 3.0-mg/kg dose ($P < .04$) and the 4.5 mg/kg dose ($P < .003$). AMPH did not significantly alter baseline motor activity measured on NOSTIM trials, but this measure was significantly increased by DOI, reflecting an effect of the highest dose ($P < .007$) (Table 2).

4. Discussion

It is axiomatic that many neuropsychiatric disorders result from inherited abnormalities in, or susceptibility to abnormalities in, specific brain mechanisms. Certain disorders are linked directly or indirectly to particular brain systems, and dysfunction in brain DA systems has been linked closely to symptoms in schizophrenia (cf., Swerdlow and Koob, 1987) and Tourette syndrome (cf., Swerdlow and Young, 1999), among other disorders. Models of inherited differences in DA function might thus be useful for understanding the genetic and neurobiological underpinnings of these disorders.

We have previously studied one such model, related to the heritable patterns of sensitivity to the PPI-disruptive effects

of the direct DA agonist APO (Swerdlow et al., 2002) in SDH and LEH rats. The present findings suggest that these heritable strain differences in PPI sensitivity: (1) are not drug-specific (i.e., occur with AMPH as well as APO) and therefore are likely to reflect physiological mechanisms with more general significance (e.g., vs. a molecule-specific transporter); (2) are seen in drugs that act via two different DAergic mechanisms (direct vs. indirect agonists) and thus, in the simplest model, reflect changes in a substrate that is impacted by each of these two different mechanisms; and (3) reflect differences within brain circuitry responsible for the DAergic but not 5HT2A regulation of PPI (and hence do not simply reflect generalized strain differences in PPI drug sensitivity).

Our aim is to understand the neurochemical basis for heritable differences in PPI drug sensitivity, rather than to identify the genes that convey these differences. To achieve this goal, we have opted to investigate outbred strains, for whom the neurochemical regulation of PPI has been well studied (cf., Geyer et al., 2001), with the key criterion being that these strains exhibit robust and heritable differences in drug sensitivity. Since nongenomic sources can be ruled out via cross-fostering (Swerdlow et al., 2003b,c), then these robust, heritable behavioral differences—even in outbred rats—presumably reflect the impact of genes on brain circuitry. Importantly, we do not view the present data to suggest that LEH rats are completely insensitive to the PPI-disruptive effects of AMPH; certainly, higher doses of AMPH might reduce PPI in these rats. Others have identified AMPH-induced reductions in PPI in LEH substrains (Feifel et al., 2001), and LEH rats are known to be sensitive to amphetamine in a number of behavioral paradigms. Still, the present data support the notion that heritable features of SDH and LEH rats produce neurochemical differences manifested in SDH>LEH sensitivity to the PPI-disruptive effects of AMPH.

What is the most parsimonious mechanism to account for heritable differences in the PPI-disruptive effects of both APO and AMPH in SDH and LEH rats? One simple explanation is that these heritable differences in PPI DA agonist sensitivity are associated with differences in NAC DA receptor density or affinity. However, in our experience and in reports from other groups, phenotypic differences in APO or AMPH sensitivity are not easily associated with differences in DA receptor density. Essman et al. (1995) reported that variations in behavioral responses to APO across five inbred rat strains could not be explained by heterogeneity of D1 or D2 receptor densities. George et al. (1991) also failed to identify differences in D1 or D2 receptor properties that could account for differences in AMPH locomotion in four inbred strains. We have found that F344 rats exhibited greater PPI APO sensitivity than do ACI rats (Shoemaker et al., 2003), but George et al. (1991) reported comparable striatal D1 and D2 receptor density and affinity in these strains. Finally, in collaborative studies with Dr. R. Luedtke, we determined that the expression of two common D2-like receptor polymorphisms (rD2Ma and rD2Mb) did not differ among SDH, N2, F1, and LEH rats (unpublished observation). Of course, other differences in DA receptor characteristics (e.g., regional distribution, including the potential involvement of DA receptors in the ventral pallidum) (Napier and Chrobak, 1992) might conceivably play a pivotal role in the "DA/PPI sensitivity" phenotype.

Alternatively, heritable differences in PPI DA agonist sensitivity might be associated, not with differences in DA receptors per se, but rather, with differences in post-DA receptor processes. In this case, the heritable substrate would not be manifested via enhanced receptor binding, but rather the substrate would be manifested via an increased *impact* of DA receptor activation on intracellular processes (e.g., G-protein coupling, etc.). This hypothesis is consistent with the notion that the heritable differences arise at a point of convergence of the mechanisms responsible for the PPI-disruptive effects of APO and AMPH, but "before" the mechanism responsible for the PPI-disruptive effects of DOI (which appears to be located within the ventral pallidum) (Sipes and Geyer, 1997).

Both schizophrenia and Tourette syndrome are heritable disorders characterized by PPI deficits (cf., Braff et al., 2001; Castellanos et al., 1996; Swerdlow et al., 2001b) and by some symptoms that—by several lines of evidence—appear to reflect states of DAergic overactivity (cf., Swerdlow and Koob, 1987; Swerdlow and Young, 1999). Thus, the SDH/LEH model of strain differences in APO PPI sensitivity recreates three features (heritability, PPI deficits, and DA activation) common to the presentations of both schizophrenia and Tourette syndrome. Certainly, the heritable substrate responsible for SDH>LEH sensitivity to the PPI-disruptive effects of DA agonists may be completely distinct from the one responsible for reduced PPI in these brain disorders. Nonetheless, using this SDH/LEH PPI model, it should be possible to identify a physiological mechanism—at or beyond the level of the mesolimbic DA receptor—through which genes control a phenotype of sensitivity to specific behavioral effects of DA stimulation. This information could be used via "backwards" analyses (to identify genes that control disorders of DA hyperfunction) or via "forwards" analyses (to identify treatments that target this specific physiological mechanism to the exclusion of other elements within brain DA systems).

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