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Locomotor-stimulating effects of indirect dopamine agonists are attenuated in Fawn hooded rats independent of postweaning social experience

F.S. Hall[a,*], G.W. Fong[a], S. Ghaed[b], A. Pert[c]

[a]*Laboratory of Clinical Studies, D.I.C.B.R., National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD 20892, USA*
[b]*Department of Psychology, University of Maryland, College Park, MD 20742, USA*
[c]*Biological Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20892, USA*

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Abstract

The effects of the indirect dopamine (DA) agonists cocaine and D-amphetamine on locomotor activity were examined in Fawn hooded (FH) rats and Wistar rats. The effect of isolation rearing was also examined to determine if it might have different effects in these two strains. Contrary to previous findings in other rat strains, only small increases in locomotor-stimulating responses to low doses of cocaine were observed in the present study as a result of isolation rearing. However, at higher cocaine doses, locomotor activity was substantially attenuated in FH rats relative to Wistar rats. A similar pattern of effects was observed for amphetamine in FH rats but only at the intermediate dose. The effects of strain and rearing were independent. There was no evidence for interactions between these factors. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Isolation rearing; Fawn Hooded rats; Dopamine; Cocaine; Amphetamine

1. Introduction

Ethanol-preferring (EP) and -nonpreferring (ENP) rat strains have been studied for some time in an effort to understand the neurochemical basis of alcoholism. Surprisingly, the role of dopaminergic systems in the purported alcoholism-modeling phenotypes characteristic of these strains has received little attention. However, there is some evidence for alterations of dopamine (DA) function in P rat strains.

Striatal or ventral striatal tissue levels of DA are increased (Alko alcohol (AA) vs. Alko nonalcohol (ANA); Kiianmaa et al., 1995), unchanged (AA vs. ANA, Sardinian P (sP) vs. Sardinian NP (sNP); Fadda et al., 1990; Korpi et al., 1988), or decreased (P vs. NP, high-alcohol drinking (HAD) vs. low-alcohol drinking (LAD); Gongwer et al., 1989; McBride et al., 1990; Murphy et al., 1983, 1987) in EP strains relative to ENP strains. The locomotor-stimulating effects of EtOH are also enhanced in some EP strains (P vs. NP, Fawn hooded (FH) vs. Wistar; Hall et al., 1998b; Waller et al., 1986) and locomotor stimulation is observed after voluntary EtOH consumption in some EP strains (A vs. ANA, sP vs. sNP; Colombo et al., 1998; Paivarinta and Korpi, 1993). Ex vivo DA metabolism after EtOH administration is enhanced in EP rats (sP vs. sNP; Fadda et al., 1991). Tissue DA metabolite levels are greater after EtOH administration in EP rats (AA vs. ANA; Fadda et al., 1990; Honkanen et al., 1994), perhaps indicating enhanced DA responsiveness. However, no differences have been observed in basal or EtOH-stimulated DA levels in the nucleus accumbens (NAC; HAD vs. LAD, AA vs. ANA; Yoshimoto et al., 1992; Yan et al., 1996). Tyrosine hydroxylase (TH) and DOPA decarboxylase activity is higher in several brain regions of AA compared to ANA rats (Pispa et al., 1986), but TH concentrations are lower in the NAC shell in P compared to NP rats (Zhou et al., 1995). More consistent findings have been observed for DA receptors. Levels of DA D_2 receptors in the striatum (Korpi et al., 1987; McBride et al., 1993; Stefanini et al., 1992) and ventral tegmental area (VTA; McBride et al., 1993) are decreased in several EP strains

* Corresponding author. Current address: Molecular Neurobiology Branch, National Institute on Drug Abuse/IRP, P.O. Box 5180, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA. Tel.: +1-410-440-2128; fax: +1-410-550-2846.

E-mail address: shall@intra.nida.nih.gov (F.S. Hall).

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compared to ENP strains (AA vs. ANA, P vs. NP, sP vs. sNP). This change is subtype-specific as D_1 and D_3 receptors are unchanged (McBride et al., 1997) at least in P vs. NP rats.

In a more direct assessment of DA involvement in enhanced ethanol consumption, P rats have been shown to self-administer EtOH directly into the VTA while NP rats will not (Gatto et al., 1994). In vivo microdialysis experiments have shown that EtOH consistently increases DA release in the NAC (Benjamin et al., 1993; Blanchard et al., 1993; Ericson et al., 1998; Heidbreder and De Witte, 1993; Wozniak et al., 1991) and the VTA (Yan et al., 1996), but no differences have been observed between EP and ENP strains (Ericson et al., 1998; Kiianmaa et al., 1995; Yoshimoto et al., 1992).

Thus, global enhancement of DA function is not consistently observed in EP rat strains, although there is evidence in some strains for enhancements. This inconsistency may reflect an underlying heterogeneity of brain mechanisms producing increased EtOH consumption in different EP rat strains, as there is heterogeneity of alcoholism in humans. This may allow the development of animal models of subtypes of alcoholism, either based symptomatically or on underlying genetic or neurochemical differences. One difficulty with developing such subtype-specific models is that there is not yet general agreement on alcoholic subtypes. However, a potentially useful typology has been proposed by Cloninger (1987): Type I associated with ''anxious'' personality traits and Type II associated with novelty-seeking traits and impaired impulse control.

With the possibility of modeling subtypes of alcoholism in mind, our laboratory has been examining two animal models of alcoholism for the past several years: the FH rat and the isolation-reared rat. Both FH (Hall et al., 1998a; Overstreet et al., 1992; Rezvani et al., 1990) and isolation-reared rats (Deatherage, 1972; Ellison, 1981; Hall et al., 1998a; Kulkosky et al., 1980; Rockman et al., 1988; Wolffgramm, 1990; Wolffgramm and Heyne, 1991) are EtOH preferring. They exhibit enhanced locomotor activity in a novel environment (Einon and Morgan, 1978; Gentsch et al., 1981; Hall et al., 1998b; Jones et al., 1989; Sahakian et al., 1982; Syme, 1973) and increased anxiety in the elevated plus maze (Hall et al., 1998b; Maisonnette et al., 1993; Wright et al., 1991), although anxiety is much more pronounced in FH rats (Hall et al., 1998b). FH isolates (FHI) also exhibit enhanced locomotor activity to low doses of EtOH, an effect that is greater than that observed in isolated Wistar rats (Hall et al., 1998b). FH rats, like isolation-reared rats, also exhibit increased acoustic startle and impaired prepulse inhibition relative to Wistar rats (Hall et al., 1997). These effects indicate alterations in mesolimbic DA systems that have not yet been examined in FH rats, although isolation rearing has been shown to enhance mesolimbic DA function and behavior associated with mesolimbic DA function (for review, see Hall, 1998). In particular, isolation rearing enhances behavioral responses to the indirect DA agonists cocaine and amphetamine (Boyle et al., 1991; Hall et al., 1998c; Jones et al., 1992, 1990; Sahakian et al., 1975; Schenk et al., 1987) and DA release after administration of indirect DA agonists assessed by in vivo microdialysis (Hall et al., 1998c; Jones et al., 1992; Wilkinson et al., 1994). If these strain and experiential effects share common mechanisms, then FH rats should also exhibit enhanced responses to indirect DA agonists such as cocaine and amphetamine. Alternatively, the mechanisms that result in enhanced EtOH responsiveness in FH rats and isolation-reared rats could be quite distinct. With this in mind, locomotor responses to the indirect DA agonists cocaine and D-amphetamine were examined.

2. Methods

2.1. Experiment 1: locomotor-stimulating effects of cocaine in socially reared and isolation-reared FH and Wistar rats

2.1.1. Subjects

FH (NCI, Frederick, MD) and Wistar (Charles River, Frederick, MD) male rats were received 21 days postnatal and were randomly divided into two rearing conditions: socially reared ($n=8$ FH rats, $n=8$ Wistar rats) and isolation-reared ($n=6$ FH rats, $n=8$ Wistar rats). These FH rats are of the FH/Har substrain (see Overstreet et al., 1996). Rats were housed with a 12:12 light/dark cycle (lights on 8 a.m.) with free access to food and water. Socially reared rats were housed in pairs per $45 \times 20 \times 20$ cm cage and isolation-reared rats were housed singly in $20 \times 20 \times 20$ cm cages. Isolation only prevented physical contact as all subjects could see, hear, and smell other rats.

2.1.2. Apparatus

After 8 weeks of housing, rats were tested for locomotor activity in Digiscan photocell activity monitors (Columbus Instruments). The chambers were constructed of clear Plexiglas (30.5 cm high $\times$ 42 cm wide $\times$ 42 cm long). The activity monitors were enclosed in sound-attenuating compartments equipped with a 15 W fluorescent light. A ventilating fan provided masking noise, and a one-way mirror mounted in the door allowed visual observation during testing. Data were recorded and stored by an IBM AT computer. This program provided total locomotor activity counts (i.e. total number of infrared beam breaks) and several measures of stereotypy (e.g. total counts, bouts, and time). Total stereotypy counts were the total of repetitive counts where one beam was interrupted without an intervening disruption of another beam. Stereotypy bouts were counted separately and defined as a series of beam breaks of the same beam, the number of breaks and duration being irrelevant. Stereotypy time was defined as the time spent repeatedly breaking the same beam rather than successive beams, which was defined as locomotion time. In Experiment 1, stereotypical behavior was also rated by an observer using the scale of Kelly et al. (1975): 0 = asleep or stationary, 1 = active,

2 = predominantly active with bursts of stereotyped sniffing or rearing, 3 = stereotyped activity predominantly sniffing or rearing over a large area of the care, 4 = stereotyped behavior maintained in one location, 5 = stereotyped behavior in one location with bursts of gnawing or licking, 6 = continual gnawing or licking. Statistical comparison of the observational and computer measures of stereotypy (the time variable) revealed a highly significant correlation ($r = .77$, $Z = 11.1$, $P < .0001$). Therefore, only the computer measures of stereotypy are presented here.

2.1.3. Procedure

Rats were first tested for novel activity and then tested on subsequent days after receiving intraperitoneal (ip) injections of saline and 5.0, 10.0, or 20.0 mg/kg cocaine for a total of five locomotor activity sessions. Dose order was counterbalanced. A minimum of 48 drug-free hours separated test days. Cocaine HCl (Sigma, St. Louis, MO) was dissolved in isotonic saline. Dosages are expressed as free base. Rats were tested in the same activity box each day. Injection was performed immediately prior to placement in the activity chambers for 60 min.

2.1.4. Statistical analysis

Summed locomotor activity scores and summed duration of stereotypical behavior were analyzed by ANOVA with the between-subjects factors of Rearing (isolation-reared vs. socially reared) and Strain (Wistar vs. FH) and the within-subjects factor of Dose (saline and 5.0, 10.0, and 20.0 mg/kg cocaine). To further specify the nature of these effects, the time course of locomotor activity for each session (the habituation session and each drug dose) was analyzed independently by ANOVA with the between-subjects factors of Strain and Rearing and the within-subjects factor of Time. Planned multiple post hoc comparisons using a Bonferroni correction were made for each dose and time point with four comparisons: FHI vs. WI, FH socials (FHS) vs. WS, WI vs. WS, and FHI vs. FHS.

2.2. Experiment 2: locomotor-stimulating effects of D-amphetamine in socially reared and isolation-reared FH and Wistar rats

2.2.1. Subjects

FH (NCI) and Wistar (Charles River) male rats were received 21 days postnatal and were randomly divided into two rearing conditions: socially reared ($N = 10$ FH rats, $N = 10$ Wistar rats) and isolation-reared ($N = 9$ FH rats, $N = 10$ Wistar rats). All subjects were housed as previously described.

2.2.2. Procedure

After 8 weeks in these housing conditions, the rats were tested for a basal activity using the apparatus previously described. Subsequently, rats were tested for locomotor activity after receiving intraperitoneal injections of saline or 0.15, 0.5, or 1.5 mg/kg D-amphetamine in the manner previously described for Experiment 1. D-amphetamine sulfate (Sigma) was dissolved in isotonic saline. Dosages are expressed as free base.

2.2.3. Statistical analysis

These data were analyzed as described previously.

3. Results

3.1. Experiment 1: locomotor-stimulating effects of cocaine in socially reared and isolation-reared FH and Wistar rats

Novelty-induced locomotor activity was significantly higher in isolation-reared compared to socially reared rats [Rearing: $F(1,26) = 7.9$, $P < .01$; Fig. 1]. Enhanced activity in isolates was attenuated by the end of the session, and the time course of this increase was somewhat different in FHI and WI rats [Time × Strain × Rearing: $F(5,130) = 2.5$, $P < .05$]. In agreement with previous work, this enhanced activity in isolates was novelty dependent. The difference was attenuated after repeated testing. Subsequently, no differences were observed between groups after saline injections (Fig. 2A).

Cocaine increased activity in a dose-dependent manner in all groups as can be seen in the locomotor activity totals (Fig. 3A). In this data, it can be seen that substantial differences in the locomotor-stimulating effects of cocaine were found between groups, which were dependent on the dose of cocaine administered [Dose × Strain: $F(3,78) = 8.8$, $P < .01$]. Although there was no overall significant effect of rearing on the locomotor activity totals, further analysis of the individual Dose × Time data revealed that after injections of 5.0 mg/kg cocaine, isolation-reared rats tended to have greater locomotor activity than socials, but this effect was not quite significant [Rearing: $F(1,26) = 4.1$, $P < .06$;

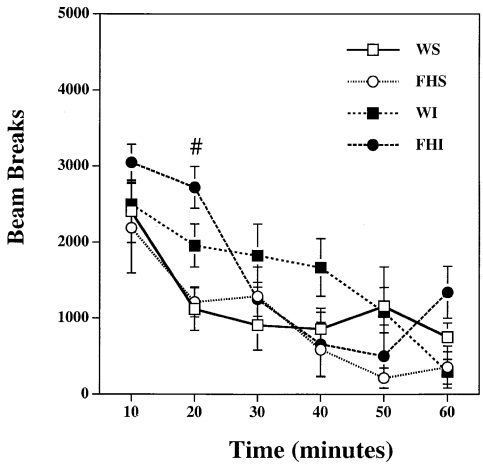

Fig. 1. Time course of locomotor activity for FHS, FHI, WI, and WS rats under novel conditions in Experiment 1. Post hoc analysis by Bonferroni-corrected t test ($P < .05$): # FHI vs. FHS.

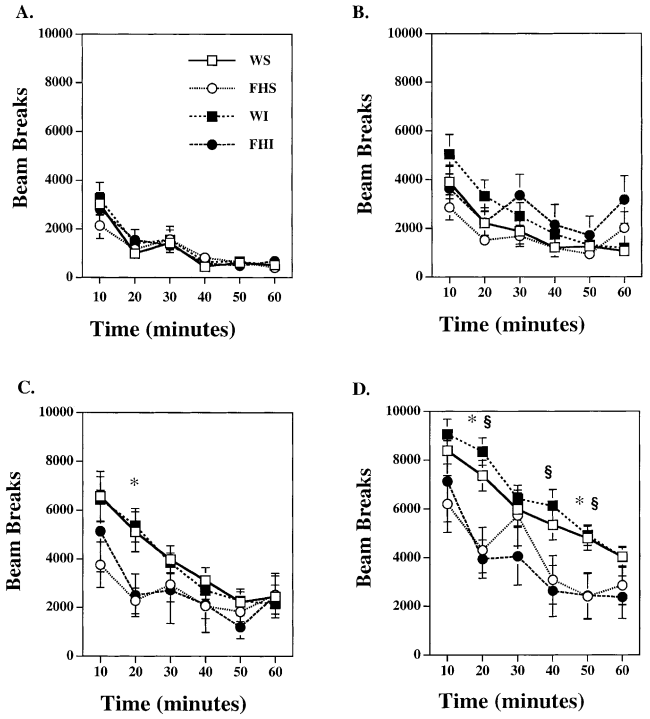

Fig 2. Time course of horizontal locomotor activity for FHI, FHS, WI, and WS rats after administration of (A) saline, (B) 5.0 mg/kg cocaine, (C) 10.0 mg/kg cocaine, and (D) 20 mg/kg cocaine. Post hoc analysis by Bonferroni-corrected t test ($P<.05$): * WS vs. FHS, § WI vs. FHI.

Fig. 2B]. With regard to Strain, Wistar rats had higher activity at this dose at the beginning of the session and FH rats had higher activity at the end of the session [Time × Strain: $F(5,130)=6.1$, $P<.01$].

A different pattern of effects was observed after injections of higher doses of cocaine where FH rats had attenuated responses. Although locomotor activity was enhanced in all groups by cocaine administration, analysis of the individual doses revealed that Wistar rats had higher levels of activity relative to FH rats after injections of both 10.0 [Strain: $F(1,26)=5.1$, $P<.05$; Fig. 2C] and 20.0 mg/kg cocaine [Strain: $F(1,26)=13.5$, $P<.01$; Fig. 2D]. Rearing was without effect at either of these doses of cocaine.

A similar pattern of effects was observed for stereotypy time (Fig. 3B). Although there was no significant effect of Rearing, isolates had a slightly longer duration of stereotypical behavior than socials at the low dose of cocaine. At higher doses of cocaine, FH rats had less stereotypical behavior than Wistar rats, independent of rearing condition [Dose × Strain: $F(3,78)=4.9$, $P<.01$]. The same pattern was observed for the observational measures (data not presented).

3.2. Experiment 2: locomotor-stimulating effects of D-amphetamine in socially reared and isolation-reared FH and Wistar rats

Basal locomotor activity levels were significantly higher in isolation-reared compared to socially reared rats [Rearing: $F(1,34)=13.0$, $P<.01$; Fig. 4], but this difference was only observed in Wistar rats [Strain × Rearing: $F(1,34)=10.9$, $P<.01$]. The activity levels of FH rats was intermediate to that of Wistar isolates (WI) and Wistar socials (WS), resulting in an interaction between Strain and Time [$F(5,170)=3.2$, $P<.01$].

Rearing differences were attenuated with repeated exposure to the apparatus so that fewer differences were observed between groups after saline injection. Isolation rearing increased locomotor activity was less than that previously observed but still significant after saline administration [Rearing × Time: $F(5,170)=2.9$, $P<.05$; Fig. 5A] as was the duration of stereotypical behavior (Fig. 6B).

D-amphetamine increased activity in a dose-dependent manner in all groups. Differences were observed between groups that were dependent on the dose of D-amphetamine administered (Fig. 5B and D). After injections of 0.15 mg/kg D-amphetamine, isolation-reared rats had greater locomotor activity than socials, but only at the beginning of the test session [Rearing × Time: $F(5,170)=2.38$, $P=.05$; Fig.

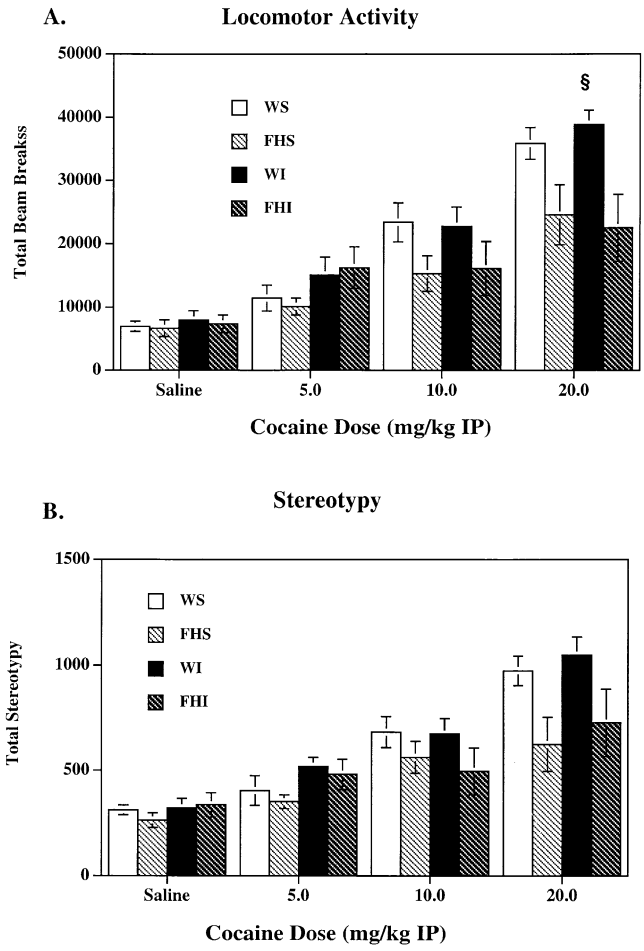

Fig 3. Total duration of stereotypical behavior for FHI, FHS, WI, and WS rats after administration of saline and 5.0, 10.0, and 20 mg/kg cocaine. Post hoc analysis by Bonferroni-corrected t test ($P<.05$): § WI vs. FHI.

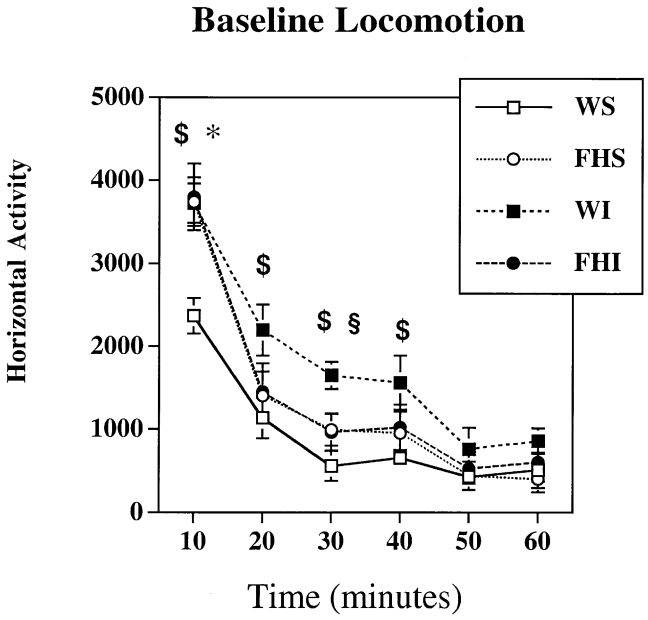

Fig 4. Time course of locomotor activity for FHS, FHI, WI, and WS rats under novel conditions in Experiment 2. Post hoc analysis by Bonferroni-corrected t test ($P<.05$): * WS vs. FHS, § WI vs. FHI, $ WI vs. WS.

5B]. However, activity after the low dose of D-amphetamine was not substantially different to that observed following saline injection.

A different pattern of effects was observed following 0.5 mg/kg D-amphetamine. Although locomotor activity was enhanced in all groups, Wistar rats had higher levels of activity relative to FH rats [Strain: $F(1,34)=6.1$, $P<.05$; Fig. 5C]. However, this effect was not observed after the high dose of D-amphetamine, although Strain interacted in a more complex way with Time [Strain × Time: $F(5,175)=6.1$, $P<.01$; Fig. 5D]. At the high dose, independent of Rearing condition, Wistar rats had enhanced locomotor activity relative to FH rats at the beginning of the test session but lower levels afterwards. Furthermore, the activity of FH rats was not affected by rearing conditions whatsoever, but WI had greater locomotor activity than WS throughout.

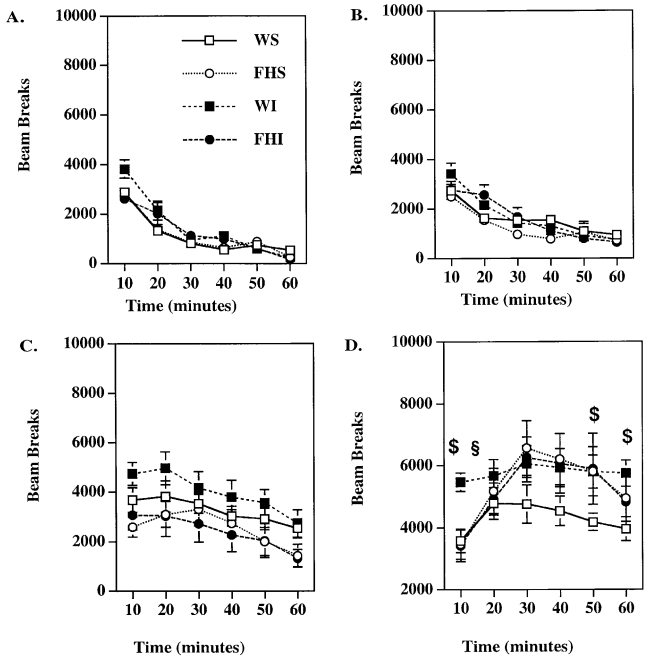

Fig 5. Time course of horizontal locomotor activity for FHI, FHS, WI, and WS rats after administration of (A) saline, (B) 0.15 mg/kg D-amphetamine, (C) 0.5 mg/kg D-amphetamine, and (D) 1.5 mg/kg D-amphetamine. Post hoc analysis by Bonferroni-corrected t test ($P<.05$): § WI vs. FHI, $ WI vs. WS.

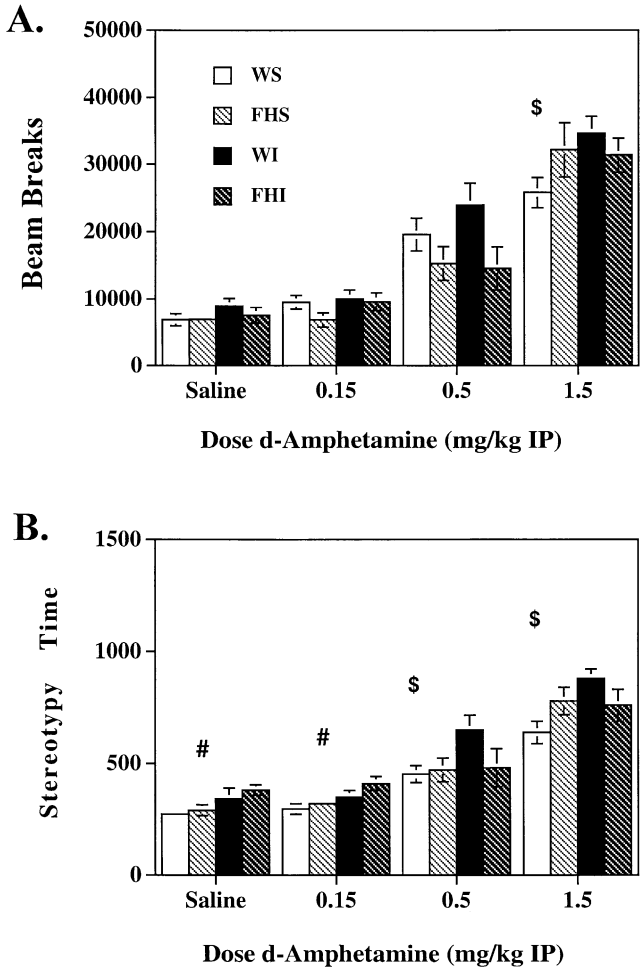

Fig 6. Total duration of stereotypical behavior for FHI, FHS, WI, and WS rats after administration of saline and 0.15, 0.5, and 1.5 mg/kg D-amphetamine. Post hoc analysis by Bonferroni-corrected t test ($P<.05$): $ WI vs. WS, # FHI vs. FHS.

A similar pattern of effects was observed for stereotypy time (Fig. 6B). Isolation-reared rats had a greater duration of amphetamine-induced stereotypy than socially reared rats [Rearing: $F(1,35)=9.5$, $P<.01$]. Again, this effect was most pronounced in Wistar rats at moderate and high doses of amphetamine [Dose × Strain × Rearing: $F(3,105)=3.2$, $P<.05$] where there was no difference between isolation-reared and socially reared FH rats.

4. Discussion

In contrast to expectation, the main finding of these experiments was that the FH rat strain is less sensitive to indirect DA agonists than the Wistar strain, although these effects were greater for cocaine than amphetamine. Decreased responses, of both locomotion and stereotypy, were observed in FH rats, relative to Wistar rats, for high doses of cocaine and the intermediate dose of D-amphetamine, which might be expected to affect primarily the DA transporter (DAT). Isolation rearing produced only modest trends toward increasing the locomotor-stimulating effects of cocaine and amphetamine in both FH and Wistar rats. This may indicate that these rat strains are less sensitive to the effects of isolation rearing than other strains commonly used in such studies (e.g. Lister Hooded rats). Therefore, although EtOH consumption is enhanced in both of these models, which might implicate similar alterations in mesolimbic DA systems, the changes in responses to indirect dopaminergic agonists are in the opposite direction.

These experiments replicated some previous observations in isolation-reared rats, including hyperactivity in a novel environment (Einon and Morgan, 1978; Gentsch et al., 1981; Jones et al., 1989; Syme, 1973) and increased locomotor-stimulating effects indirect DA agonists (Einon and Sahakian, 1979; Jones et al., 1990; Phillips et al., 1993). This experiment also replicated the previous observations in FH rats of hyperactivity (Hall et al., 1998b), although these effects are quite variable for unknown reasons (e.g. Fig. 1 FHI > WI, Fig. 4 FHS > WS). However, observation of hyperactivity in FH rats is highly situation dependent. This appears to be the result of profound anxiety in this strain that interferes with the expression of locomotor hyperactivity.

A main purpose of these experiments was to determine the sensitivity of FH rats to indirect DA agonists. Contrary to expectation, at moderate to high doses of cocaine, FH rats actually exhibited smaller increases in locomotor activity than Wistar rats. By contrast, FH rats were less sensitive to amphetamine only at the intermediate dose. This may indicate that FH rats are less sensitive to DA uptake blockers but not DA releasers, implicating alterations in the DAT but not the vesicular monoamine transporter (VMAT). At low doses, amphetamine, and other releasing agents, may act as both reuptake blockers and releasers, but at higher doses the releasing effects predominate (Seiden et al., 1993). An alternative suggestion might be that FH rats have enhanced stereotypical behavior after indirect DA agonist administration, resulting in decreased locomotor responses, but similar patterns were observed for both locomotion and stereotypy effectively negating this hypothesis.

The differing mechanisms producing altered sensitivity to indirect DA agonists in these models have important implications for other associated behavioral and pharmacological phenotypes. In FH rats, decreased sensitivity to these drugs may be the result of decreased number of reuptake sites or reduced affinity for cocaine and/or DA. Although such a state would reduce sensitivity to DA reuptake blockers that act directly through this site, such as cocaine, it would increase sensitivity to compounds that increase dopaminergic activity through other means by prolonging the actions of released DA. EtOH affects DA release through diverse mechanisms, but it has been shown to increase DA cell firing in the VTA and substantia nigra (Brodie and Appel, 1998; Brodie et al., 1999a,b, 1990; Mereu et al., 1984). Decreased DA reuptake would also increase sensitivity to other stimuli that produce increased DA release by elevating DA cell firing and would therefore account for behavioral effects in FH rats thought to be reflective of enhanced DA function (Hall et al., 1997, 1998a,b).

Another characteristic of FH rats, or at least the FH/Har substrain (Overstreet and Rezvani, 1996), is increased anxiety (Hall et al., 1998b, in press-a) and associated enhancements of plasma corticosterone after exposure to stressful environments (Hall et al., in press-a, in press-b). Enhanced anxiety would most closely parallel Cloninger's (1987) Type I alcoholics, as would diminished responses to stimulant drugs but enhanced responses to sedative drugs (Cloninger, 1998). Although this hypothesis is very preliminary, the FH rat, in some important respects, may model the proposed Type I alcoholic subtype. It remains for future research to determine the strength of this model, for instance, whether there is a gender interaction such as that described for Type I alcoholics (Gilligan et al., 1988). Since alcoholism is a heterogeneous disorder, heterogeneity of animal models based on phenotypic, or genotypic, similarities to human subtypes will better model the disease.

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