

Risperidone Exerts Potent Anti-aggressive Effects in a Developmentally Immature Animal Model of Escalated Aggression

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Background: Risperidone has been shown to be clinically effective for the treatment of aggressive behavior in children, yet no information is available regarding whether risperidone exhibits aggression-specific suppression in preclinical studies that use validated developmentally immature animal models of escalated aggression. Previously, we have shown that exposure to low doses of the psychostimulant cocaine-hydrochloride (.5 mg/kg intraperitoneally) during the majority of pubertal development (postnatal days [P]27–57) generates animals that exhibit a high level of offensive aggression. This study examined whether risperidone exerts selective aggression-suppressing effects by using this pharmacologic animal model of highly escalated offensive aggression.

Methods: Experimental hamsters were tested for offensive aggression after the acute administration of risperidone (.05–1.0 mg/kg, intraperitoneally).

Results: Risperidone dose-dependently reduced the highly aggressive phenotype, with a significant reduction observed at .1–.2 mg/kg for most aggressive responses measured. Experimental animals treated with higher doses of risperidone (.3–1.0 mg/kg) showed significant reductions in aggression and social interest toward intruders, indicating more general behavioral inhibition.

Conclusions: These studies provide evidence that risperidone exerts specific aggression-suppressing effects in a developmentally immature animal model of escalated aggression.

Key Words: Adolescence, cocaine, development, risperidone, Syrian hamsters

Although aggressive behaviors in children and adolescents are common, normative, and serve an important evolutionary purpose (Connor 2002), aggression in psychiatrically referred youngsters is often considered maladaptive in that it occurs in circumstances that are independent of an expected social context or in the absence of expected social cues (Bambauer and Connor 2005; Steiner *et al.* 2003). Because early-onset maladaptive aggression can be very difficult to treat and accounts for high rates of hospitalization, institutionalization, and psychopharmacological use, it remains an important area of study (Connor *et al.* 1997; Connor 2002; Findling *et al.* 2005).

Atypical antipsychotics increasingly are being used as pharmacologic treatments for aggression in a variety of child and adolescent psychiatric disorders (Schur *et al.* 2003). For example, aripiprazole, olanzapine, quetiapine, and ziprasidone each have demonstrated effectiveness for aggressive behavior in select populations of aggressive children (Findling *et al.* 2005). The atypical antipsychotic risperidone, however, has been the best-studied drug to date for aggressive behavior in psychiatrically referred children and adolescents (Findling *et al.* 2005). For instance, in 5- to 15-year-old males with conduct disorder,

risperidone was effective relative to treating symptoms of aggression at a mean dose of 1.26 mg/d (oral dosing) or of $.028 \pm .004$ mg/kg per day (Findling *et al.* 2000), whereas in autistic children 5 to 17 years old, risperidone was effective and well tolerated for the treatment of tantrums, aggression, and self-injurious behaviors (Research Units on Pediatric Psychopharmacology Autism Network 2002), at doses ranging between .5 and 3.5 mg/d (weight-corrected doses not given). Similarly, in several studies of irritable and aggressive children with subaverage intelligence, risperidone was effective for the treatment of severely disruptive behaviors, conduct problems, and aggression (Aman *et al.* 2002; Van Bellinghen and De Troch 2001) in doses ranging between .02 and .06 mg/kg per day.

Because risperidone increasingly is used to treat aggression in children and adolescents, we chose to investigate this atypical antipsychotic in a developmentally sensitive, preclinical animal model of escalated aggression. The use of preclinical models of aggression affords the possibility of examining the pharmacologic response to more specific types of aggression than typically is found in clinical studies that often combine multiple types of aggressive behaviors into a single omnibus measure of aggression. Clinical research is attempting to identify and validate more specific subtypes of aggression in children and adolescents, such as proactive and reactive aggression (Connor 2002; Vitiello and Stoff 1997). Proactive aggression is overcontrolled, planned, predatory, and driven by reward contingencies, whereas reactive aggression generally is characterized by an overaroused and impulsive response to a threatening stimulus (Connor 2002). Although not an exact fit, offensive aggression in animals possesses many of the characteristics of reactive aggression in human beings (Bambauer and Connor, 2005; Blanchard and Blanchard 2003; Moyer 1977), including impulsive responding and intense aggression focused on a specific object identified as threatening. The identification of aggression subtypes is important because the brain mechanisms that subservise different subtypes of aggression are distinct in animals (Eichelman 1992) and in human beings (Blair

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2004), and appropriate dose responses to pharmacologic interventions may differ across aggression subtypes. For the most part, the preclinical studies that have examined the effects of risperidone on aggression have not been sensitive to this important distinction. Indeed, in several reports in which risperidone was found to be an effective agent for the reduction of isolation- and apomorphine-induced aggression, active drug had to be administered at comparatively high doses (risking side effects on motor behavior) or in combination with other agents sharing similar receptor-binding profiles (Rodriguez-Arias *et al.* 1998; Skrebuhova-Malmros *et al.* 2000). In studies using genetic mutants, however, risperidone was found to reduce isolation-induced aggression at relatively low doses, such as .03–.1 mg/kg (Moechars *et al.* 1998). In each of these studies, however, risperidone's effects on aggression were examined in adult animals and were not investigated using developmentally sensitive models that possibly equate to human children and adolescents. Presently, no information is available regarding whether risperidone exhibits aggression-specific suppression in preclinical studies that use validated, developmentally immature animal models of offensive aggression. This information is critical if clinicians are to be confident that risperidone exerts aggression-selective effects with possible relevance for human children and adolescents.

Recently, we have established and validated a pharmacologic model to study the behavioral and developmental neurobiology of escalated offensive aggression by using immature Syrian hamsters (*Mesocricetus auratus*); (DeLeon *et al.* 2002; Harrison *et al.* 2000; Jackson *et al.* 2005; Knyshevski *et al.* 2005a, 2005b; Melloni *et al.* 2001; Ricci *et al.* 2004, 2005). In this model, repeated exposure to extremely low doses of the psychostimulant cocaine-hydrochloride (.5 mg/kg intraperitoneally) during puberty (P27–57) generates late-pubertal animals that exhibit high levels of offensive aggression. These animals show no changes in social communication, sexual motivation, or general motor activity, indicating that the treatment regimen has specific aggression-eliciting effects. This pharmacologic model is particularly useful for the study of escalated aggression in developmentally immature animals for several reasons. First, experimental animals tested during late puberty display a highly escalated offensive phenotype characterized by short attack and bite latencies, high intensity and frequency of offensive acts, and prolonged aggressive bouts, as defined by Miczek *et al.* (2003). This escalated level of offensive aggression exceeds that of experienced adult fighters (i.e., hamsters trained to respond aggressively by repeated exposure to conspecifics) that are stimulated to respond hyperaggressively by the direct activation of neural circuits stimulating aggression (Ferris *et al.* 1997), suggesting that aggression may be maximized in this model. Second, experimental animals display mature, adult forms of offensive aggression in the absence of social-learning cues and established social interactions, suggesting that the treatment paradigm directly activates neural mechanisms controlling this phenotype. This distinction is critical because the use of this model may then allow for a direct examination and manipulation of the neural components subserving offensive aggression. Indeed, in subsequent studies, we showed that the offensive phenotype in experimental animals is modulated by serotonin (5HT) neural signaling and development (DeLeon *et al.* 2002; Knyshevski *et al.* 2005a, 2005b; Ricci *et al.* 2004), that is, a neural signal shown to inhibit aggression in human beings and animals (Nelson and Chiavegatto 2001), including hamsters (Delville *et al.* 1996; Ferris *et al.* 1997, 1999). Together, these data support

the notion that deficient 5HT development or activity may underlie escalated offensive aggression in this immature animal model. These findings support those from studies in adolescent and adult human beings and a number of animal models that implicate a link between 5HT hypofunction and escalated impulsive, reactive subtypes of aggression (Brown *et al.* 1979, 1982; Ho *et al.* 2001; Kyes *et al.* 1995; Mehlman *et al.* 1994; Vergnes *et al.* 1988).

Given accumulating evidence that risperidone may reduce escalated impulsive, reactive aggression observed in child and adolescent psychiatric populations, it is important to determine whether risperidone has potent, anti-aggressive properties when administered preclinically to developmentally immature animal models that display highly escalated offensive aggression. These studies use our pharmacologic adolescent-animal model of escalated offensive aggression to examine the hypothesis that acute risperidone treatment during puberty can reduce the highly escalated offensive-aggressive phenotype.

Methods and Materials

Animals

In Syrian hamsters, the pubertal period of development can be approximated as the time between P25 and P60. Weaning generally occurs around P25, with the onset of puberty (as determined by the onset of gonadal maturation) around P30 (Miller *et al.* 1977). Testosterone levels start to rise at around P30, reaching near peak levels by P45 and finally peaking between P50 and P55 (Melloni *et al.* 1997b; Miller *et al.* 1977). During this developmental time period, hamsters wean from their dams, leave the home nest, establish new, solitary nest sites, and learn to defend their territory and participate in social-dominance hierarchies (Schoenfeld and Leonard 1985; Whitsett 1975).

For the experimental treatment paradigm, intact pubertal male hamsters (P21) were obtained from Charles River Laboratories (Wilmington, Massachusetts), individually housed in Plexiglas cages, and maintained at ambient room temperature on a reverse light–dark cycle (14 hours light and 10 hours dark; lights on at 6:00 PM). Food and water were provided *ad libitum*. For aggression testing, stimulus (intruder) males of equal size and weight to the experimental animals were obtained from Charles River 1 week before the behavioral test, group-housed at five animals per cage in large polycarbonate cages, and maintained as just described to acclimate to the animal facility. All intruders were prescreened for a low level of social interest (i.e., disengage and evade) and environmental fear responses (i.e., tail-up freeze, flee, and fly-away) 1 day before the aggression test to control for behavioral differences between stimulus animals, as described elsewhere (Melloni *et al.* 1997a; Ricci *et al.* 2004; Ricci 2005). Intruders displaying significantly low aggression or submissive postures (<5%) were excluded from use in the behavioral assay. All methods and procedures described in the following two sections were preapproved by the Northeastern University Institutional Animal Care and Use Committee (NU-IACUC).

Aggression Testing

We tested experimental animals for offensive aggression by using the resident–intruder paradigm, a well-characterized and ethologically valid model of offensive aggression in Syrian hamsters (Floody and Pfaff 1977; Lerwill and Makaings 1971). Briefly, an intruder of similar size and weight was introduced into the home cage of the experimental animal (resident), and the resident was scored for either (1) general measures of offensive

aggression (i.e., number of attacks and bites, latency to attack and bite toward intruders) as described elsewhere (Harrison *et al.* 2000) or (2) more specific and targeted aggressive responses including upright offensive postures, lateral attacks, aggressive pursuits, head or nape bites, and flank or rump bites, as described elsewhere (Grimes *et al.* 2003), to provide a more detailed account of the aggressive encounter between residents and intruders. An attack was scored each time that the resident animal would pursue and then either (1) lunge toward or (2) confine the intruder by upright and sideways threat, each generally followed by a direct attempt to bite the intruder's dorsal rump or flank target areas. Composite aggression scores, used as a broad measure of offensive aggression, were defined as the total number of attacks (i.e., upright offensives and lateral attacks) and bites (i.e., head or nape and flank or rump bites) during the behavioral test period. The latency to attack and bite was defined as the period of time between the beginning of the behavioral test and the first attack and bite of the residents toward an intruder. In the case of no attacks or bites, latencies were assigned the maximum time of the test duration (i.e., 600 sec). In addition, residents were measured for social interest toward intruders (i.e., contact time between resident and intruder), and the frequency of social investigation (i.e., sniffing) and grooming bouts were counted to control for nonspecific effects of risperidone on animal behavior. Contact time was defined as the period of time during which the resident initiated contact with the intruder, whether through social investigation (e.g., sniffing), or aggression. Each aggression test lasted for 10 min and was videotaped and coded manually by two observers who were unaware of the hamsters' experimental treatment. Differences in scores for all behaviors measured were less than 5% between the two observers. No intruder was used for more than one behavioral test, and all animals were tested during the first 4 hours of the dark cycle under dim-red illumination to control for circadian influences on behavioral responding.

Experimental Treatment

Pubertal (P27) Syrian hamsters ($n = 84$) received daily intraperitoneal injections of low-dose (.5 mg/kg) cocaine hydrochloride for 30 consecutive days (P27–P57), as described elsewhere (DeLeon *et al.* 2002; Harrison *et al.* 2000; Ricci *et al.* 2004, 2005). The day after the last injection (P58), experimental animals were randomly assigned to one of six treatment groups ($n = 10$ –12 animals per group) and were tested for offensive aggression after an intraperitoneal injection of saline or one of five doses (.05, .1, .2, .3, or 1.0 mg/kg) of risperidone. All injections were performed on unanesthetized animals and took no longer than 10 sec. After injection, animals were returned to their home cage. Thirty min later, animals were tested for offensive aggression as described elsewhere. The dose range for risperidone was selected on the basis of previous reports indicating dose-response efficacy in human beings. As a baseline (i.e., nonaggressive) behavioral control, a separate set of hamsters ($n = 10$) was treated with saline throughout adolescence and was tested for aggression in parallel with the risperidone-treated animals.

Statistical Analysis

Results from the aggression tests were compared across treatment conditions. All behaviors were compared by using one-way analysis of variance, followed by Fisher's probable least squares difference post hoc (two-tailed) test when applicable. The α level for all experiments was set at .05.

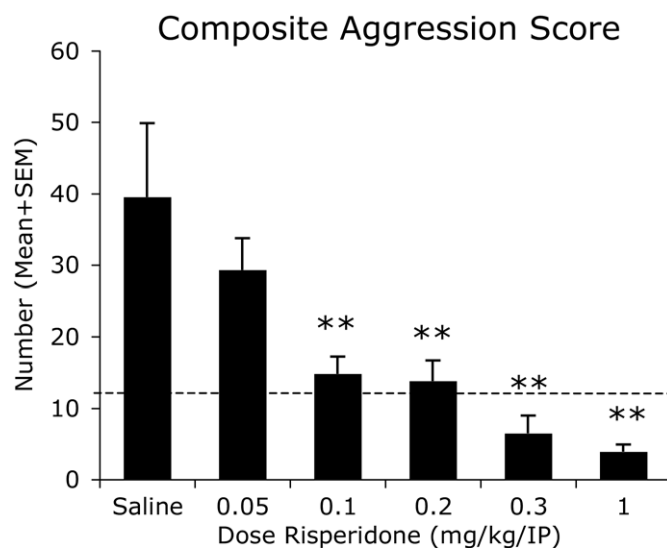


Figure 1. Effects of risperidone on composite aggression scores (i.e., a broad measure of aggression intensity). Risperidone treatment (.05–1.0 mg/kg intraperitoneally [IP]) dose dependently decreases composite aggression in experimental animals. The dashed line represents the baseline behavioral response of nonaggressive (i.e., noncocaine) controls. Bars denote SEM. ** $p < .01$.

Results

Systemic administration of risperidone produced an overall effect on aggression intensity, as measured by composite scores of offensive aggression (i.e., total number of attacks and bites; $[F(6,69) = 8.32, p < .0001]$, with anti-aggressive effects significant beginning at the .1-mg/kg dose and continuing to the 1.0-mg/kg dose. At these doses, risperidone treatment significantly reduced composite aggression [.1 mg/kg, $t(20) = 3.64$; .2 mg/kg, $t(21) = 3.79$; .3 mg/kg, $t(20) = 4.75$; and 1.0 mg/kg, $t(21) = 5.36$; $p < .01$ for each comparison] of aggressive animals toward intruders when compared with control animals (Figure 1). Similarly, risperidone produced a separate overall effect on offensive attack [$F(6,69) = 6.85, p < .0001$] and bite behavior [$F(6,69) = 4.71, p < .01$] within the same effective anti-aggressive dose range. At these doses, risperidone treatment significantly decreased the number of total attacks [.1 mg/kg, $t(20) = 3.24$; .2 mg/kg, $t(21) = 3.13$; .3 mg/kg, $t(20) = 3.32$; and 1.0 mg/kg, $t(21) = 3.26$; $p < .01$ for each comparison] and bites [.1 mg/kg, $t(20) = 2.03, p < .05$; .2 mg/kg, $t(21) = 3.07, p < .01$; .3 mg/kg, $t(20) = 3.29, p < .01$; and 1.0 mg/kg, $t(21) = 3.96, p < .01$] of aggressive animals toward intruders when compared with controls (Figure 2). Similarly, at higher doses of risperidone, there was a significant decrease in the number of attacks and bites of aggressive animals toward intruders when compared with lower doses of risperidone [attacks: .05 vs. .1, $t(22) = 2.20, p < .05$; .05 vs. .2, $t(22) = 2.08, p < .05$; .05 vs. .3, $t(22) = 3.28, p < .01$; and .05 vs. 1.0, $t(22) = 3.77, p < .01$; bites: .05 vs. .2, $t(22) = 2.72, p < .01$; .05 vs. .3, $t(22) = 2.96, p < .01$; and .05 vs. 1.0, $t(22) = 3.63, p < .01$].

Conversely, at all doses within the effective anti-aggressive range, risperidone failed to produce an overall effect on the initiation of the aggressive interaction, as measured by the latency to first attack [$F(6,68) = .67, p = .67$] (Figure 2). However, an overall effect was observed on latency to bite [$F(6,68) = 4.4, p < .001$] (Figure 2). Here, risperidone treatment significantly delayed the onset of biting behavior toward intrud-

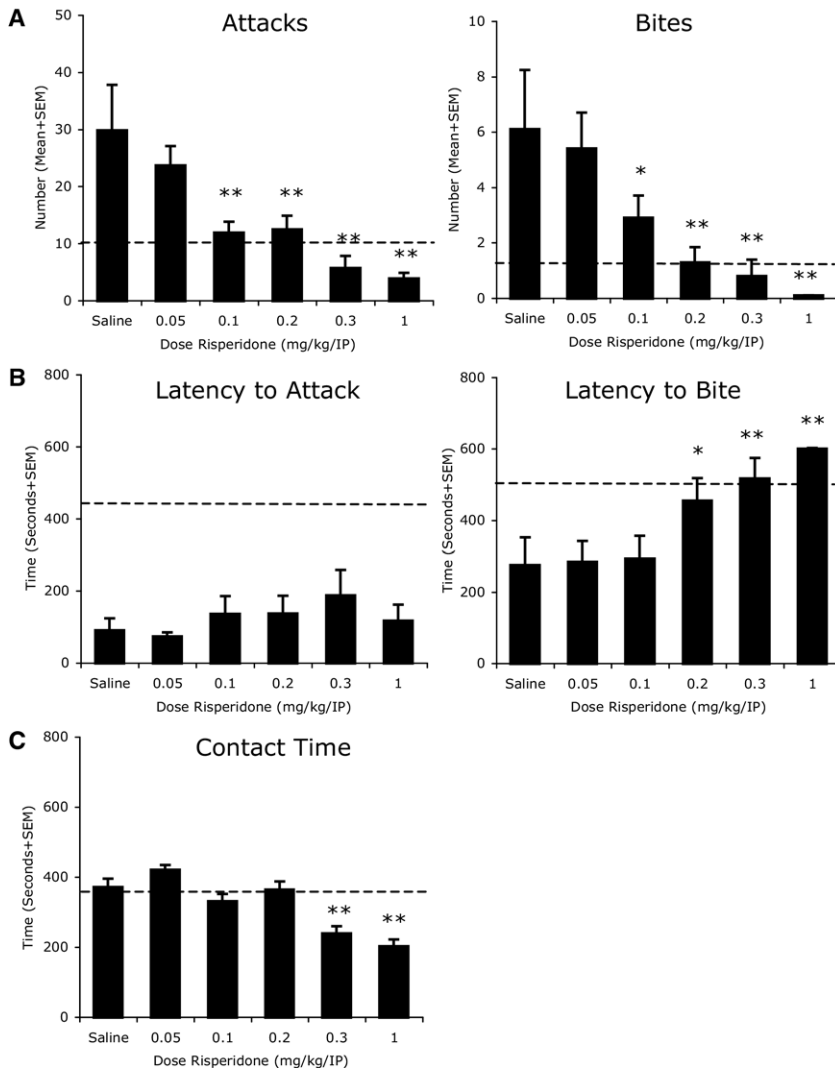


Figure 2. Effects of risperidone on offensive aggression. (A) Risperidone treatment (.05–1.0 mg/kg) produces a dose-dependent decrease in measures of aggression intensity (i.e., number of attacks and bites) in cocaine-treated residents, whereas (B) aggression initiation (i.e., mean latency to first bite) is affected only at doses that reduce social interest (i.e., contact time), as in (C). Dashed lines (A–C) represent the baseline behavioral response of nonaggressive (i.e., noncocaine) controls. IP, intraperitoneally. Bars denote SEM. * $p < .05$, ** $p < .01$.

ers, with an effective dose range beginning at .2 mg/kg [.2 mg/kg, $t(21) = 2.07$, $p < .05$; .3 mg/kg, $t(20) = 2.79$, $p < .01$; and 1.0 mg/kg, $t(21) = 3.71$, $p < .01$]. Further analysis showed that systemic administration of risperidone produced a significant effect on total contact time [$F(6,68) = 12.7$, $p < .0001$; i.e., a measure of social interest] during the behavioral test (Figure 2). Animals in higher dose treatment groups (i.e., .3 mg/kg and above) spent less time engaged with intruders during the behavioral test than did saline-treated controls [.3 mg/kg, $t(20) = 4.08$, $p < .01$ and 1.0 mg/kg, $t(21) = 5.47$, $p < .01$]. However, the systemic administration of risperidone at doses below (i.e., .3 mg/kg) and within the lower anti-aggressive range (i.e., .1–.2 mg/kg) failed to produce any significant differences in contact time when compared with saline-treated controls [.05 mg/kg, $t(21) = 1.57$, $p > .05$; .1 mg/kg, $t(20) = 1.25$, $p > .05$; and .2 mg/kg, $t(21) = .20$, $p > .05$]. Similarly, within this dose range (i.e., .05–.2 mg/kg), risperidone failed to produce a significant effect on social investigation [$F(4,47) = .41$, $p = .80$; e.g., sniffing of intruders] or self-grooming (a comfort measure) [$F(4,47) = 1.50$, $p = .22$] during the behavioral test (Figure 3).

When the lower anti-aggressive range was examined more precisely, risperidone produced an overall effect on several specific and targeted offensive responses. In particular, systemic administration of risperidone produced an overall effect

on the number of lateral attacks [$F(6,68) = 8.54$, $p < .0001$], flank or rump bites [$F(6,68) = 4.54$, $p < .001$], and aggressive pursuits, with significant effects observed at the .1- and .2-mg/kg doses (Figure 4). At these doses, risperidone administration significantly reduced the number of lateral attacks [.1 mg/kg, $t(20) = 4.37$, $p < .01$ and .2 mg/kg, $t(21) = 4.69$, $p < .01$], flank or rump bites [.1 mg/kg, $t(20) = 3.26$, $p < .01$ and .2 mg/kg, $t(21) = 3.42$, $p < .01$], and aggressive pursuits [.1 mg/kg, $t(20) = 2.93$, $p < .01$ and .2 mg/kg, $t(21) = 2.72$, $p < .01$], compared with hamsters treated with saline before aggression testing.

Similarly, at the effective doses of risperidone (i.e., .1 and .2 mg/kg), there were significant decreases in the number of lateral attacks of aggressive animals toward intruders when compared with the lowest dose (i.e., .05 mg/kg) of risperidone [.05 vs. .1, $t(21) = 2.71$, $p < .01$; and .05 vs. .2, $t(22) = 3.04$, $p < .01$]. The same was true for the lowest dose (i.e., .05 mg/kg) of risperidone when compared with the effective doses (i.e., .1 mg/kg and .2 mg/kg), with respect to flank or rump bites [.05 vs. .1, $t(21) = 2.14$, $p < .05$ and .05 vs. .2, $t(22) = 2.30$, $p < .05$] and aggressive pursuits [.05 vs. .1, $t(21) = 2.56$, $p < .05$ and .05 vs. .2, $t(22) = 2.35$, $p < .05$]. However, at the effective doses, risperidone failed to produce any significant differences in upright offensive attacks, when compared with saline-treated controls [.1 mg/kg,

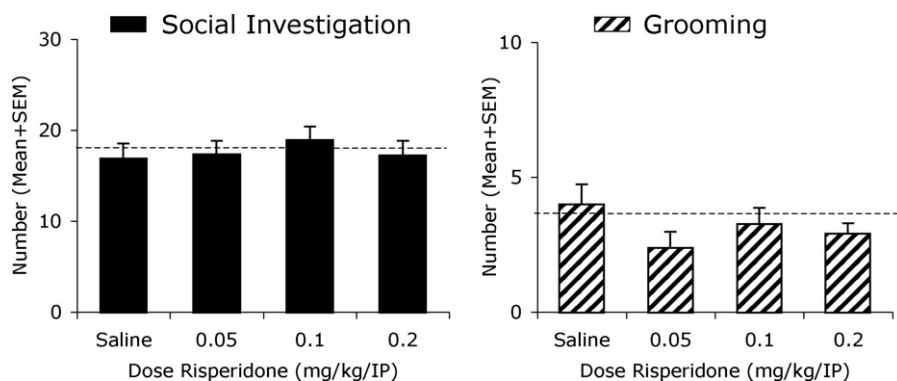


Figure 3. Effects of risperidone on social and comfort behaviors. Risperidone treatment (.05–.2 mg/kg intraperitoneally [IP]) has no effect on social investigation or grooming in aggressive, experimental residents. Dashed lines represent the baseline behavioral response of nonaggressive (i.e., noncocaine) controls. Bars denote SEM.

$t(20) = 1.54, p > .05$ and $.2$ mg/kg, $t(21) = 1.13, p > .05$] or lower doses of risperidone [.05 vs. .1, $t(21) = .97, p > .05$ and .05 vs. .2, $t(22) = .55, p > .05$].

Discussion

We report results from a fixed-dose behavioral pharmacology study examining the effects of risperidone on a well-validated developmentally immature animal model of highly escalated offensive aggression. In this model, animals pretreated with a low-dose cocaine-treatment regimen, that is, a stimulus known to result in the compromised development of the 5-HT neural system (DeLeon *et al.* 2002; Ricci *et al.* 2004), displayed a highly escalated offensive aggressive phenotype (DeLeon *et al.* 2002; Harrison *et al.* 2000; Jackson *et al.* 2005; Knyshevski *et al.* 2005a, 2005b; Melloni *et al.* 2001; Ricci *et al.* 2004, 2005). Results show that risperidone reduced the highly escalated offensive aggressive phenotype in a dose-dependent manner, with a significant reduction in aggression observed at .1–.2 mg/kg for most aggressive responses measured. At this dose, anti-aggressive effects of risperidone were observed without concomitant effects on comfort stereotypies (i.e., grooming) and social behavior (i.e., contact times), suggesting a specific offensive aggression-suppressing effect of risperidone.

The behavioral data presented in this report support our hypothesis that risperidone may serve as an effective treatment strategy for an escalated offensive phenotype. For instance, aggressive experimental animals administered saline before behavioral testing displayed high levels of offensive aggression, analogous to that observed in our previous studies (DeLeon *et al.* 2002; Harrison *et al.* 2000; Jackson *et al.* 2005; Knyshevski *et al.* 2005a, 2005b; Melloni *et al.* 2001; Ricci *et al.* 2004, 2005) and presented here (Figures 1, 2, and 4). Nearly all (10 of 12) saline-treated animals showed a high intensity of aggression (as defined by targeted attack and bite scores and a quick onset (initiation) of the aggressive response (defined by the latency to first attack and bite). Conversely, administration of risperidone to aggressive, experimental animals before behavioral testing dose-dependently reduced aggressive responding. Risperidone-treated hamsters showed a greater than 65%–75% decrease in attacks and bites at .1 mg/kg when compared with saline-treated counterparts. Because acute risperidone dose-dependently reduced only certain aspects of the aggressive response (i.e., aggression intensity but not initiation), it was possible that risperidone was acting in a highly discriminating anti-aggressive fashion, with selective effects on specific and targeted measures of the offensive aggressive response.

To address this issue, the anti-aggressive properties of risperidone were investigated, examining several more specific and targeted determinates of offensive aggression. Specifically, consistent with the decrease in the number of attack and bites, at the low effective dose (i.e., .1 mg/kg), risperidone-treated animals showed a greater than 50% decrease in the number of lateral attacks, flank or rump bites, and aggressive pursuits, compared with saline-treated controls. No effect of risperidone at either of the effective doses was noted on upright offensive attacks, nape bites, nor latency to first attack and/or bite. This finding is interesting given that bites targeted toward the flank or rump region of the intruder have been shown to be intense and highly organized, mature aspects of the aggressive phenotype (Delville *et al.* 2003; Wommack and Delville 2003). The highly selective nature of risperidone's anti-aggressive properties, combined with the lack of any effect on contact time, social investigation, and grooming, indicated that risperidone did not attenuate aggressive responding through general nonspecific behavioral inhibition or sedation. Thus, these data suggest that risperidone treatment may be effective at attenuating the intensity level of the adult offensive-aggressive phenotype in developmentally immature animals, perhaps by virtue of its actions on select brain systems and regions that are implicated in the control of aggression.

These findings may have relevance for early-onset maladaptive aggression in referred children and adolescents. As noted in the introductory section of this article, well-validated animal models of offensive aggression (Moyer 1977) have similarities with characteristics of the reactive subtype of aggression frequently found in psychiatrically referred youngsters, including impulsive responding and intense aggressive behaviors directed at an identified threat object (Connor *et al.* 2004). That risperidone appears to have a specific effect on offensive aggression in our animal model suggests that further delineation of aggression subtypes in preclinical as well as clinical studies may yield the possibility of more specific psychopharmacological interventions in the future. To achieve this goal, further research investigating just how animal subtypes of aggression map onto human subtypes of aggression urgently is needed to move the field forward and facilitate translational aggression research.

However, human aggression is much more complex than can be captured in a highly defined animal model of aggression. The role of psychiatric diagnosis may be additionally important in psychiatrically referred children and adolescents. For example, there is evidence that stimulants reduce aggression in human beings with the ADHD phenotype (Connor *et al.* 2002). The interplay of aggression subtype and psychiatric diagnosis in the

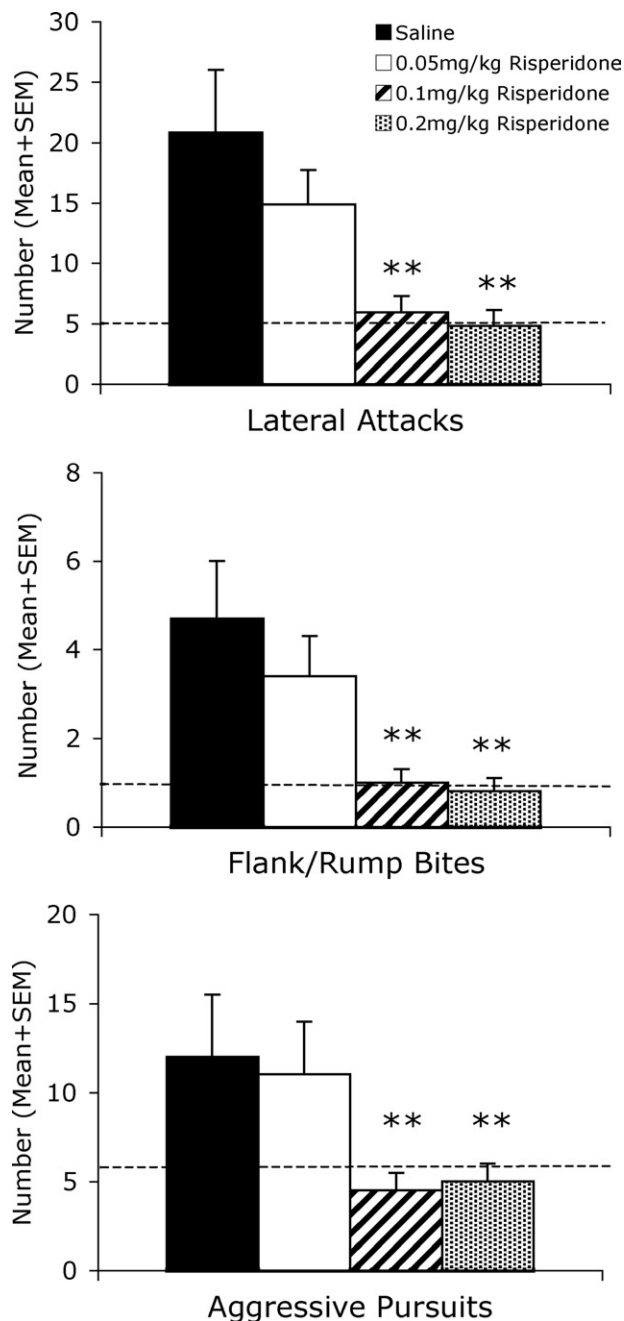


Figure 4. Effects of risperidone on select offensive responses. Risperidone treatment (.05–2 mg/kg intraperitoneally [IP]) dose dependently decreases specific and targeted measures of aggression intensity (i.e., number of lateral attacks, flank or rump bites, and aggressive pursuits) in aggressive experimental animals. Dashed lines represent the baseline behavioral response of nonaggressive (i.e., noncocaine) controls. Bars denote SEM. ** $p < .01$.

etiology of maladaptive early-onset aggression is an area in need of further clinical research.

A number of neural systems and neurochemical signals have been implicated in aggression control. In particular, the serotonin (5HT) and dopamine (DA) neural systems have been implicated in the regulation of aggressive behavior. A wealth of data supports an inverse relationship between 5HT activity and aggression (Brown *et al.* 1979, 1982; Higley *et al.* 1992; Kyes *et al.*

1995; Mehlman *et al.* 1994; Miczek *et al.* 1974; Olivier *et al.* 1989; Vergnes *et al.* 1988), and manipulations that elevate 5HT (Auerbach *et al.* 1989; Ferris 1996; Guan and McBride 1988; Perry and Hughes 1992) serve to suppress aggression (Dalta *et al.* 1991; Molina *et al.* 1987; Ogren *et al.* 1980; Olivier *et al.* 1989; Sanchez and Hyttel 1994; Villalba *et al.* 1997). The importance of specific 5HT receptors, namely the 5HT 1A, 1B, and 2A subtype receptors, as mediators of the aggressive response has been demonstrated (Albonetti *et al.* 1996; Bell *et al.* 1995; Cologer-Clifford *et al.* 1997; de Boer *et al.* 1999; Ferris *et al.* 1999; Fish *et al.* 1999; Joppa *et al.* 1997; McMillen *et al.* 1987; Miczek *et al.* 1998; Mos *et al.* 1992; Olivier *et al.* 1989, 1995; Pfeffer *et al.* 1997; Ratey *et al.* 1991; Ricketts *et al.* 1994; Sakaue *et al.* 2002; Sanchez *et al.* 1993; Sanchez and Hyttel 1994; Saudou *et al.* 1994; Sijbesma *et al.* 1990, 1991; Verhoeven and Tuinier 1996; White *et al.* 1991). For instance, activation of 5HT_{2A} receptors with selective 5HT_{2A} agonists increase aggressive behavior (Sakaue *et al.* 2002), whereas blockade using selective 5HT_{2A} antagonists and mixed 5HT_{2A} and DA D₂ receptor antagonists reduces aggression (Sakaue *et al.* 2002; Sanchez *et al.* 1993; Shih *et al.* 1999; Skrebuhhova-Malmros *et al.* 2000). Similarly, blockade of DA D₂ subtype receptors using selective DA D₂ antagonists or the genetic deletion of the long form of the DA D₂ receptor (D_{2L}) has been shown to reduce aggressive behavior (Arregui *et al.* 1993; Navarro and Manzaneque 1997; Nikulina and Kapralova 1992; Vukhac *et al.* 2001), although at higher doses this reduction is associated with significant impairment of other motor behaviors. Conversely, activation of DA D₂ receptors with selective agonists increases defensive behavior, social fearfulness, and anxiety (Gendreau *et al.* 2000; Navarro and Maldonado 1999; Sweidan *et al.* 1991). Taken together, the ability of these agents to modulate aggression emphasizes the role of 5HT and DA acting through 5HT_{1A/B}, 5HT_{2A}, and DA D₂ receptors as important molecular components of the neural circuit that serves to control aggression.

Risperidone is a monoaminergic antagonist with high affinity for the 5HT_{2A} (.71 nM) and DA D₂ (5.9 nM) receptors and possesses both serotonergic and dopaminergic properties. It is frequently used in child and adolescent psychiatry for a variety of neuropsychiatric disorders. In children and adolescents with excessive, inappropriate aggressive behavior within the context of several psychiatric diagnoses, risperidone demonstrates anti-aggressive effects (Aman *et al.* 2002; Findling *et al.* 2000; Research Units on Pediatric Psychopharmacology Autism Network 2002; Van Bellinghen and De Troch 2001). Our preclinical behavioral data presented here are important and novel in that they indicate that risperidone's anti-aggressive properties can be extended across species to well-validated, developmentally immature animal models of offensive aggression and suggest that the specificity of risperidone's effects on this aggression subtype in animals may complement data in children and adolescents. This suggests that risperidone may possess targeted anti-aggressive effects. Further study of risperidone and other atypical antipsychotics in the treatment of maladaptive aggression across well-validated aggression subtypes and in psychiatric diagnoses with a high prevalence of aggressive behaviors is warranted in both preclinical and clinical studies.

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