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Repeated risperidone administration during puberty prevents the generation of the aggressive phenotype in a developmentally immature animal model of escalated aggression

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ABSTRACT

Risperidone has been shown to be clinically effective for the treatment of aggressive behavior in children, yet until recently no information was available regarding whether risperidone exhibits aggression-specific suppression in preclinical studies employing validated developmentally immature animal models of escalated aggression. Recently, using a pharmacologic animal model of escalated offensive aggression, we reported that acute risperidone treatment selectively and dose-dependently reduces the expression of the adult aggressive phenotype, with a significant reduction in aggressive responses observed at 0.1 mg/kg, i.e., a dose within the range administered to children and adolescents in the clinical setting. This study examined whether repeated exposure to risperidone during puberty would prevent the generation of the highly escalated aggressive phenotype in this animal model. To test this hypothesis, the aggression-eliciting stimulus (i.e., cocaine hydrochloride, 0.5 mg/kg/day×28 days) was co-administered with an aggression-suppressing dose of risperidone (i.e., 0.1 mg/kg/day) during different time frames of puberty and for varied lengths of time (i.e., 1–4 weeks), and then animals were scored for targeted measures of offensive aggression during late puberty. Risperidone administration prevented the generation of the adult aggressive phenotype, with a complete blockade of matured offensive responses (i.e., lateral attacks and flank/rump bites) seen only after prolonged periods of exposure to risperidone (i.e., 3–4 weeks). The selective prevention of these aggressive responses, while leaving other measures of aggression intact (e.g., upright offensive postures), suggest that risperidone is acting in a highly discriminatory anti-aggressive fashion, targeting neurobehavioral elements important for the mature aggressive response pattern.

1. Introduction

Atypical antipsychotics are increasingly being used as pharmacological treatments for aggression in a variety of child and adolescent psychiatric disorders [1]. For example, aripiprazole, olanzapine, quetiapine, and ziprasidone have each demonstrated effectiveness for aggressive behavior in select populations of aggressive children [2]. The atypical antipsychotic risperidone, a dopamine (DA) D2 and serotonin (5HT) 2A antagonist, has been the best-studied drug to date for aggressive behavior in psychiatrically referred children and adolescents [2]. For instance, risperidone has been shown to be clinically effective for the treatment of severely disruptive behaviors, conduct problems, tantrums, self-injurious behaviors and the symptoms of aggression in a range of child and adolescent patient populations with doses ranging from approximately 0.02 to 0.08 mg/kg/day [3–6].

Since risperidone is increasingly used to treat aggression in children and adolescents, we chose to investigate the aggression-suppressing effect of this atypical antipsychotic in a validated developmentally-sensitive animal model of escalated aggression being careful to include dose response relationships that best approximate those used in clinical practice. In this model, Syrian hamsters (*Mesocricetus auratus*) repeatedly exposed to low doses of the psychostimulant cocaine hydrochloride (0.5 mg/kg, IP) during puberty (P27–56) exhibit high levels of the matured offensive response characterized by short attack latencies and high intensity and frequency of offensive acts targeted to the flank and rump region of conspecifics when tested during late puberty (P57) [7–15]. These animals display this matured form of offensive aggression in the absence of social learning cues and established social interactions, suggesting that the treatment paradigm directly activates neurobehavioral mechanisms controlling the adult behavioral phenotype. In

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recent studies, we showed that acute risperidone treatment selectively and dose-dependently reduced the expression of the matured aggressive phenotype displayed by animals using this model, with a significant reduction in aggressive responses observed at 0.1 mg/kg [16], i.e., a dose within range of that administered to children and adolescents in the clinical setting. For the most part, other preclinical studies that have examined the effects of risperidone on aggression have not been sensitive to this important distinction. Indeed, in several reports where 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 [17,18]. In studies using transgenic mice however, risperidone was found to reduce isolation-induced aggression at relatively low doses, i.e., 0.03–0.1 mg/kg [19]. In each of these studies, however, risperidone's effects on aggression were examined following acute administration of the drug and not investigated using repeated treatment regimens that possibly equate to those prescribed to human children and adolescents.

Indeed, in recent clinical studies risperidone has been found to be an effective treatment for escalated aggression in child and adolescent patients at doses ranging from 0.02–0.08 mg/kg/day for a minimum of 4 weeks, with a range of treatment times spanning 1 month to 2 years [3,5,6,20–22]. Since puberty is arguably the most critical developmental period during which youth are at risk for aggression, it would be important to determine whether short- or long-term risperidone treatment during this period acts as an effective prophylactic against the generation (or further development) of the highly aggressive phenotype. And if so, what is the minimum duration and critical period during puberty that risperidone has its most effective anti-aggressive effects? Unfortunately, whether repeated risperidone treatment during this developmental period would be an effective agent for the suppression of the aggressive phenotype has not been adequately studied in human populations or in preclinical studies employing pubertal animal models. To this end, these studies utilize our developmentally-sensitive, pharmacologic animal model of escalated offensive aggression to examine the hypothesis that repeated risperidone treatment during puberty can suppress the development of the highly aggressive behavioral phenotype.

2. Methods

2.1. Animals

In Syrian hamsters, the pubertal period of development can be approximated as the time between postnatal days 25 and 65 (P25–P65). Weaning generally occurs around P25 with the onset of puberty (as determined by the onset of gonadal maturation) beginning around P30 [23]. Testosterone levels start to rise at around P30, reaching near peak levels by P45 and finally peaking between P50 and 55 [23,24]. 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 [25,26].

For the experimental treatment paradigm, intact pubertal male hamsters (P21) were obtained from Charles River Laboratories (Wilmington, MA), individually housed in Plexiglas cages, and maintained at ambient room temperature on a reverse light:dark cycle (14L:10D; lights on at 19:00). 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 one week prior to the behavioral test, group housed at 5 animals/cage in large polycarbonate cages, and maintained as above 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) one day prior to the aggression test to control for behavioral differences between stimulus animals, as previously described [9,11,27,28]. Intruders displaying significantly low interest and/or submissive postures (<5%) were excluded from use in the behavioral assay. All methods and procedures described below were pre-approved by the Northeastern University Institutional Animal Care and Use Committee (NU-IACUC).

2.2. Aggression testing

Experimental animals were tested for offensive aggression using the resident–intruder paradigm, a well-characterized and ethologically valid model of offensive aggression in Syrian hamsters [29,30]. Briefly, an intruder of similar size and weight was introduced into the home cage of the experimental animal (resident) and the resident was

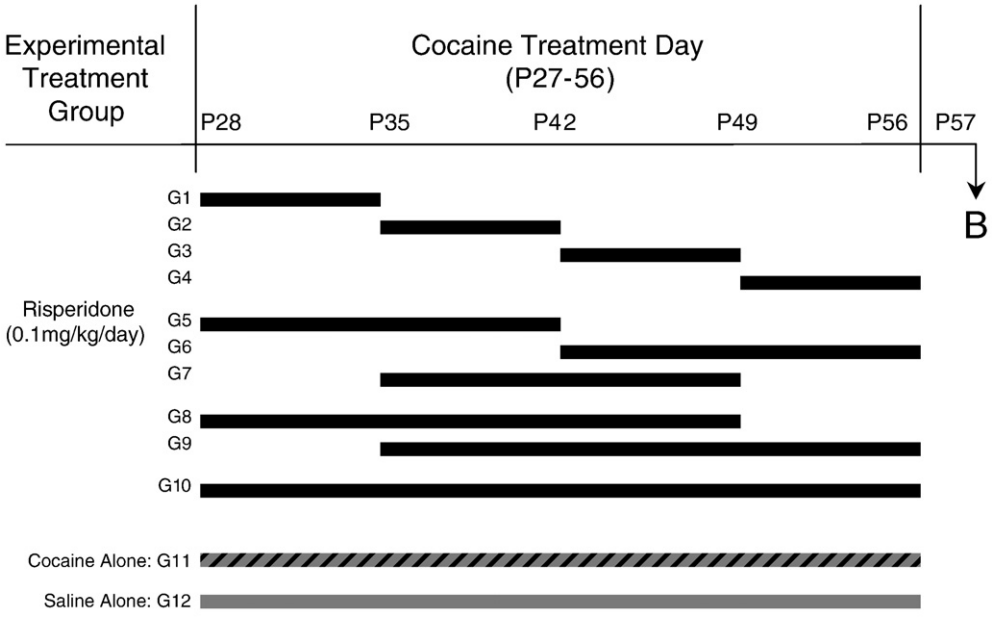

Fig. 1. Diagram showing the experimental treatment paradigm. Hamsters were administered cocaine hydrochloride (0.5 mg/kg/day) during pubertal development (postnatal [P] days 27–56, then tested for aggressive, social, grooming, and wall climbing behavior (i.e., Behavior testing [B]) on P57. Animals in groups [G] 1–10 received daily intraperitoneal [IP] injections of cocaine, followed by an IP injection of risperidone (0.1 mg/kg/day for varied durations during pubertal development [i.e., 1 week (G1–4), 2 weeks (G5–7), 3 weeks (G8–9), or 4 weeks (G10)]). Control animals in G11 and G12 were treated with cocaine or saline alone throughout puberty and tested for aggression in parallel with the above animals.