HHS Public Access

Author manuscript

Behav Pharmacol. Author manuscript; available in PMC 2016 July 29.

Published in final edited form as:

Behav Pharmacol. 2015 June ; 26(4): 393–397. doi:10.1097/FBP.0000000000000136.

Cocaine self-administration punished by intravenous histamine in adolescent and adult rats

Nathan A. Holtz and **Marilyn E. Carroll**

Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota, USA

Abstract

Adolescence is a transitional phase marked by a heightened vulnerability to substances of abuse. It has been hypothesized that both increased sensitivity to reward and decreased sensitivity to aversive events may drive drug-use liability during this phase. To investigate possible age-related differences in sensitivity to the aversive consequences of drug use, adolescent and adult rats were compared on self-administration of cocaine before, during, and after a 10-day period in which an aversive agent, histamine, was added to the cocaine solution. Adult and adolescent female rats were trained to self-administer intravenous cocaine (0.4 mg/kg/infusion) over 10 sessions (2 h/session; 2 sessions/day). Histamine (4 mg/kg/infusion) was then added directly into the cocaine solution for the next 10 sessions. Finally, the cocaine/histamine solution was replaced with a cocaine-only solution, and rats continued to self-administer cocaine (0.4 mg/kg) for 20 sessions. Compared with adolescent rats, adult rats showed a greater decrease in cocaine self-administration when it was punished with intravenous histamine compared with their baseline cocaine self-administration rates. These results suggest that differences in the sensitivity to negative consequences of drug use may partially explain developmental differences in drug use vulnerability.

Keywords

adolescence; cocaine; histamine; punishment; rat; self-administration

Introduction

The initiation of substance-use disorders primarily occurs during adolescence (Nixon and McClain, 2010). Although environmental factors are likely to contribute to this phenomenon, adolescence is also characterized by a unique neurobiological profile that may render individuals particularly vulnerable to drug use (Chambers *et al.*, 2003; Kuhn *et al.*, 2010). This concept has been supported by preclinical research indicating that adolescent rats, compared with adults, self-administer more methamphetamine (Anker *et al.*, 2012), cocaine (Schramm-Sapyta *et al.*, 2011; Holtz and Carroll, 2013), and nicotine (Nesil *et al.*,

Correspondence to Nathan A. Holtz, PhD, Rush University, 1735 W Harrison, Room 454, Chicago, IL 60612, USA, holt0324@umn.edu.

Conflicts of interest

There are no conflicts of interest.

2011) and that they exhibit greater reinstatement of drug-seeking, using an animal model of relapse (Anker and Carroll, 2010).

The greater propensity for substance abuse in adolescents than in adults may be the result of a heightened sensitivity to rewarding events, as well as an attenuated sensitivity to aversive events during this phase. For instance, adolescent rats are more sensitive to the conditioned rewarding effects of nicotine (Vastola *et al.*, 2002; Shram *et al.*, 2006; Torres *et al.*, 2008), ethanol (Philpot *et al.*, 2003), and cocaine (Brenhouse and Andersen, 2008) compared with adult rats. Conversely, adolescent rats show less sensitivity to the aversive aspects of lithium chloride (Schramm-Sapyta *et al.*, 2006), as well as multiple drugs of abuse, such as tetrahydrocannabinol (Schramm-Sapyta *et al.*, 2007), cocaine (Schramm-Sapyta *et al.*, 2006), morphine (Hurwitz *et al.*, 2012), ethanol (Vetter-O'Hagen *et al.*, 2009; Anderson *et al.*, 2010), acute nicotine exposure (Wilmouth and Spear, 2004), and precipitated nicotine withdrawal (O'Dell *et al.*, 2006, 2007). However, the majority of these studies examined the aversive effects of these substances using conditioned taste aversion, and the interpretation of data from this paradigm continues to be disputed (Grigson, 2008; Huang and Hsiao, 2008; Liu *et al.*, 2009).

Thus, the present study examined the role of age-related sensitivity to aversive events during drug self-administration, by punishing cocaine self-administration with concurrent intravenous infusions of the noxious agent histamine. Adult and adolescent rats were trained to self-administer intravenous cocaine, and then histamine was added directly to the cocaine solution. Intravenous histamine administration is an effective punisher of operant responding for both drug and non-drug rewards in nonhuman primates (Goldberg, 1980; Negus, 2005; Woolverton *et al.*, 2012). Peripheral histamine administration may also mimic or enhance some of the aversive, interoceptive aspects of protracted drug use – namely, neurological pruritus (Weisshaar *et al.*, 2009; Liu *et al.*, 2010; Angst *et al.*, 2012). Recent work has shown that adult rats selected for high (vs. low) drug-abuse vulnerability were less sensitive to histamine punishment of cocaine self-administration (Holtz *et al.*, 2013). The present study comparing adolescent and adult rats differed from the previous study in that adult rats used an accelerated procedure that involved a nose-poke (vs. previously used lever press) response and two 2 h sessions per day (vs. 1 2 h session in previous the study) to accommodate the short period of adolescence in the rats. In humans, it has been reported that adolescents are generally less sensitive to aversive events compared with adults (Spear, 2009; Vetter-O'Hagen *et al.*, 2009; Doremus-Fitzwater *et al.*, 2010); thus, the hypothesis of the present study was that adults would self-administer less cocaine compared with adolescents when histamine was present in the cocaine solution compared with basal cocaine intake.

Methods

Subjects

Adolescent (n =12) and adult (n = 9) female rats served as subjects in this study. Both groups were bred from unrelated, outbred Wistar rats (Harlan Sprague–Dawley, Indianapolis, Indiana, USA) bred in our laboratory. Adolescent rats began the study during postnatal days (PND) 23–29, while adult rats began the study during PND 92–102. The

mean (± SEM) ages of adolescent and adult rats at the beginning of the study were 25.3 (± 0.6) and 95.0 (± 1.1) days, respectively, and the mean (± SEM) ages of adolescent and adult rats on the last day of the study were 69.8 (± 2.5) and 137.3 (± 3.0) days, respectively. The beginning of the study was defined as the day of catheter implantation surgery, and the end was defined as the day on which the last self-administration session occurred. Adolescent and adult rats were tested for an average of 44.6 (± 2.7) and 42.5 (± 3.3) days, respectively. The younger group of rats is referred to as adolescents, although, by the end of the study, the rats transitioned from a generally agreed upon span of adolescence (~ PND 50) to an age range that may be considered adolescence to early adulthood (~PND 75). Animal-housing conditions are described in the study by Holtz *et al.* (2013). Experimental procedures were approved by The University of Minnesota Institutional Care and Use Committee under Protocol #1007A85632, and they complied with the Guide for the Care and Use of Laboratory Animals [National Research Council (U.S.). Committee for the Update of the Guide for the Care and Use of Laboratory Animals., Institute for Laboratory Animal Research (U.S.), National Academies Press (U.S.), 2011].

Apparatus

Following catheter implantation surgery [for details, see the study by Holtz *et al.* (2013)], and throughout the experiment, rats were housed in custom-made, octagon-shaped operant conditioning chambers as described elsewhere (Carroll *et al.*, 1981), with the exception that the response manipulanda in the present experiment were nose-poke devices (vs. levers in Carroll *et al.*, 1981) equipped with internal infrared beams and stimulus lights (Med Associates, St Albans, Vermont, USA). Responses occurred when an animal's nose entered the apparatus and interrupted the infrared beam. A response on one nose-poke device (i.e. an active response) resulted in the delivery of a cocaine infusion and the illumination of the stimulus light inside the apparatus for the duration of the infusion. A response on the other nose-poke device (i.e. an inactive response) resulted in the illumination of the stimulus light within that device; however, an infusion was not delivered. Programming, data collection, and data storage for all experimental sessions were handled by Med-PC software and PCs equipped with a Med-PC interface (Med Associates).

Procedure

Rats were trained to self-administer intravenous cocaine (0.4 mg/kg/infusion) during daily 6 h sessions. Once the stable self-administration criteria were met, rats completed two daily 2 h sessions throughout the rest of the experiment (9 a.m.–11 a.m., 1 p.m.–3 p.m.). The first phase (prehistamine) lasted 10 sessions. Next, rats began the histamine phase in which histamine (4 mg/kg/infusion) was added directly into the cocaine solution for 10 sessions. Last was the posthistamine phase in which the cocaine/histamine solution was replaced with a histamine-free cocaine solution for 20 sessions.

Data analysis

Cocaine infusions and responses on the inactive nose-poke apparatus (inactive responses) served as the dependent measures in this study. Either measures were averaged for each animal in blocks of five sessions (eight total blocks, see Fig. 1). These data were analyzed with two-way (age × block), mixed-factorial, repeated-measures analyses of variance. Age

(adolescents vs. adults) was the between-subjects factor, and block (1–8) was the within-subjects, repeated-measures factor. After finding a significant interaction term, post-hoc analyses were conducted with Fisher's protected least significant difference procedure. If significant main effects were found in the absence of interaction effects, post-hoc analyses were conducted using the Tukey–Kramer honestly significant difference procedure. Block 2 served as the comparison measure of baseline cocaine self-administration within subjects. Changes in self-administration were also analyzed during the histamine and posthistamine phases, relative to prehistamine cocaine self-administration, by computing percentage change of average infusions self-administered during blocks 3–8 compared with block 2 [(block 2 infusions − block *x* infusions)/(block 2 infusions) × 100]. This procedure was also applied to inactive responses. Thus, percentage change of average infusions or inactive responses served as the dependent measure in this analysis. Percentage changes in infusions or inactive responses for each histamine (blocks 3 and 4) and posthistamine (blocks 5–8) block were compared between groups using Student's *t*-tests. Grubb's test (GraphPad Software, La Jolla, California, USA) was used to detect outlying data points that were excluded from analyses. All other tests were conducted with GB Stat software (Dynamic Microsystems, Silver Spring, Maryland, USA), and results were considered significant if the *P* value was less than 0.05.

Results

Figure 1 shows cocaine infusions self-administered by adult and adolescent rats throughout the experiment. There was a significant main effect of block ($F_{7,133} = 13.6$, $P < 0.0001$), whereas there was no significant effect of age, nor age × block interaction. Post-hoc analyses indicated that adolescent rats self-administered fewer cocaine infusions during block 4 of the histamine phase compared with adolescents on block 2 (baseline; $P < 0.05$), whereas adults self-administered fewer cocaine infusions during blocks 3 ($P < 0.05$) and 4 ($P < 0.01$) of the histamine phase compared with adults on block 2. However, there were no significant differences in cocaine self-administration between adolescent and adult rats throughout the experiment. A significant block × age interaction was found for inactive responses ($F_{7,133} = 2.5$, $P < 0.05$; data not shown): adults made significantly more inactive (unreinforced) responses compared with adolescents during blocks 1, 4, and 8 ($P < 0.05$). Figure 2 illustrates that adult rats showed a significantly greater percentage decrease in baseline cocaine infusions during the first five-session block of the histamine phase compared with adolescent rats ($t_{19} = 3.9$, $P < 0.001$). There were no differences in percentage change of inactive responses compared with baseline between the groups.

Discussion

Results from the present experiment indicate that the punishing effects of histamine on intravenous cocaine self-administration were initially greater in adult rats than in adolescent rats. These results corroborate previous studies in which adolescent animals have exhibited decreased sensitivity to aversive events compared with adult rats (O'Dell *et al.*, 2006, 2007; Schramm-Sapyta *et al.*, 2006, 2007; Vetter-O'Hagen *et al.*, 2009; Anderson *et al.*, 2010; Hurwitz *et al.*, 2012). Moreover, the results agree with a more general trend in which more drug-abuse prone animals tend to be less aversion-sensitive than those exhibiting resistance

to drugs of abuse. For instance, rats that have been selectively bred for high saccharin intake also show a greater avidity for drugs and less sensitivity to aversive events compared with animals bred for low saccharin intake (Carroll *et al.*, 2008). In contrast, low saccharin intake rats show greater signs of ethanol withdrawal (Dess *et al.*, 2005) and emotional reactivity to other aversive events (Dess *et al.*, 2000) compared with high saccharin intake rats. Similar to the relatively less drug-vulnerable adults (vs. adolescents) examined in the present study, we have recently shown that low saccharin intake rats are more sensitive to histamine-punished cocaine self-administration (Holtz *et al.*, 2013). Although there are important procedural differences between these studies (e.g. levers vs. nose-poke devices, one vs. two daily sessions, respectively), together the results suggest that, a fundamental characteristic of the etiology of substance-use disorders is the negative relationship between drug use vulnerability and aversion sensitivity (Riley, 2011; Shabani *et al.*, 2011; Barkley-Levenson *et al.*, 2013).

Although histamine was more effective at punishing cocaine self-administration in adult rats than in adolescent rats, this effect was only present during the first half of histamine treatment and may be considered transient. Future studies could investigate whether other doses of histamine would elicit more or less differential punishment effects between adolescent and adult rats. Furthermore, we cannot rule out that this difference was mediated by factors other than a general variance in sensitivity to aversive events. For instance, the well-established age-mediated variance in drug metabolism (Strolin-Benedetti and Baltes, 2003) may explain the present results; that is, histamine may be eliminated more rapidly in adolescents, in effect decreasing the circulating histamine dose relative to adults.

In the present study, using the nose-poke response, in contrast to some past experiments on individual differences and drug consumption (Schramm-Sapyta *et al.*, 2011; Holtz *et al.*, 2013), there were no age differences in baseline cocaine intake. Furthermore, although adult rats made more nonreinforced responses (inactive nose-pokes) over multiple phases of the present study, previous work using a similar self-administration procedure (active vs. inactive lever response) has often reported that adolescent rats made more nonreinforced responses compared with adult rats (Frantz *et al.*, 2007; Anker and Carroll, 2010; Anker *et al.*, 2012). These inconsistencies may be explained by differences in the type of response operandum used in these studies (i.e. nose-pokes in present study vs. levers in past studies), as such differences can engender dramatically divergent patterns of drug self-administration (Clemens *et al.*, 2010). Although nonreinforced responding often serves as a proxy for general activity levels, or impulsive behavior (Cummins and Leri, 2008), future studies may investigate differences in the development of prepotent responses (nose-poking) and other operant-behavior modalities (lever pressing, wheel turning, etc.) between adult and adolescent rats, and how this may relate to age differences in drug use liability.

Conclusion

The present results suggest that adult rats are affected to a greater extent compared with adolescent rats by the punishing effects of intravenous histamine when it was added to a cocaine self-administration solution. From a translational perspective, these data may inform pharmacological strategies for treating substance-use disorders that act by enhancing the

aversive consequences of drug consumption. Disulfiram is one such agent that has been applied to ethanol, opiate, and cocaine addiction (McCance-Katz *et al.*, 1998; Jorgensen *et al.*, 2011). Although the aversive consequences of intravenous histamine-punished drug consumption are likely to be qualitatively different than those elicited by disulfiram, our results suggest that a punishment-type of therapeutic approach may be better suited to adult rats than adolescent rats. Future research should expand on these findings and investigate possible age-related differences in other treatment strategies, such as those that reduce (i.e. baclofen) or replace (i.e. modafinil) some of the effects of abused drugs.

Acknowledgments

The authors are grateful for the technical assistance of Seth Johnson and Amy Saykao. This research was supported by grants R01 DA019942 and K05 DA015267 (MEC).

References

Anderson RI, Varlinskaya EI, Spear LP. Ethanol-induced conditioned taste aversion in male Sprague–Dawley rats: impact of age and stress. Alcohol Clin Exp Res. 2010; 34:2106–2115. [PubMed: 20860618]

Angst MS, Lazzeroni LC, Phillips NG, Drover DR, Tingle M, Ray A, et al. Aversive and reinforcing opioid effects: a pharmacogenomic twin study. Anesthesiology. 2012; 117:22–37. [PubMed: 22713632]

Anker JJ, Carroll ME. Reinstatement of cocaine seeking induced by drugs, cues, and stress in adolescent and adult rats. Psychopharmacology (Berl). 2010; 208:211–222. [PubMed: 19953228]

Anker JJ, Baron TR, Zlebnik NE, Carroll ME. Escalation of methamphe-tamine self-administration in adolescent and adult rats. Drug Alcohol Depend. 2012; 124:149–153. [PubMed: 22305912]

Barkley-Levenson AM, Cunningham CL, Smitasin PJ, Crabbe JC. Rewarding and aversive effects of ethanol in high drinking in the dark selectively bred mice. Addict Biol. 2013; 20:80–90. [PubMed: 23910826]

Brenhouse HC, Andersen SL. Delayed extinction and stronger reinstatement of cocaine conditioned place preference in adolescent rats, compared to adults. Behav Neurosci. 2008; 122:460–465. [PubMed: 18410184]

Carroll ME, France CP, Meisch RA. Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. J Pharmacol Exp Ther. 1981; 217:241–247. [PubMed: 6112257]

Carroll ME, Morgan AD, Anker JJ, Perry JL, Dess NK. Selective breeding for differential saccharin intake as an animal model of drug abuse. Behav Pharmacol. 2008; 19:435–460. [PubMed: 18690102]

Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry. 2003; 160:1041–1052. [PubMed: 12777258]

Clemens KJ, Caille S, Cador M. The effects of response operandum and prior food training on intravenous nicotine self-administration in rats. Psychopharmacology (Berl). 2010; 211:43–54. [PubMed: 20437028]

Cummins E, Leri F. Unreinforced responding during limited access to heroin self-administration. Pharmacol Biochem Behav. 2008; 90:420–427. [PubMed: 18479741]

Dess NK, Arnal J, Chapman CD, Siebel S, VanerWeele DA, Green KF. Exploring adaptations to famine: rats selectively bred for differential intake of saccharin differ on deprivation-induced hyperactivity and emotionality. Int J Comp Psychol. 2000; 13:34–52.

Dess NK, O'Neill P, Chapman CD. Ethanol withdrawal and proclivity are inversely related in rats selectively bred for differential saccharin intake. Alcohol. 2005; 37:9–22. [PubMed: 16472715]

Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. Brain Cogn. 2010; 72:114–123. [PubMed: 19762139]

Frantz KJ, O'Dell LE, Parsons LH. Behavioral and neurochemical responses to cocaine in periadolescent and adult rats. Neuropsychopharmacology. 2007; 32:625–637. [PubMed: 16794567]

Goldberg SR. Histamine as a punisher in squirrel monkeys: effects of pentobarbital, chlordiazepoxide and H1- and H2-receptor antagonists on behavior and cardiovascular responses. J Pharmacol Exp Ther. 1980; 214:726–736. [PubMed: 6105208]

Grigson PS. The state of the reward comparison hypothesis: theoretical comment on Huang and Hsiao (2008). Behav Neurosci. 2008; 122:1383–1390. [PubMed: 19045958]

Holtz NA, Carroll ME. Escalation of i.v. cocaine intake in peri-adolescent vs. adult rats selectively bred for high (HiS) vs. low (LoS) saccharin intake. Psychopharmacology (Berl). 2013; 227:243–250. [PubMed: 23307070]

Holtz NA, Anker JJ, Regier PS, Claxton A, Carroll ME. Cocaine self-administration punished by i.v. histamine in rat models of high and low drug abuse vulnerability: effects of saccharin preference, impulsivity, and sex. Physiol Behav. 2013; 122:32–38. [PubMed: 23948673]

Huang AC, Hsiao S. Re-examination of amphetamine-induced conditioned suppression of tastant intake in rats: the task-dependent drug effects hypothesis. Behav Neurosci. 2008; 122:1207–1216. [PubMed: 19045940]

Hurwitz ZE, Merluzzi AP, Riley AL. Age-dependent differences in morphine-induced taste aversions. Dev Psychobiol. 2012; 55:415–428. [PubMed: 22585679]

Jorgensen CH, Pedersen B, Tonnesen H. The efficacy of disulfiram for the treatment of alcohol use disorder. Alcohol Clin Exp Res. 2011; 35:1749–1758. [PubMed: 21615426]

Kuhn C, Johnson M, Thomae A, Luo B, Simon SA, Zhou G, et al. The emergence of gonadal hormone influences on dopaminergic function during puberty. Horm Behav. 2010; 58:122–137. [PubMed: 19900453]

Liu C, Showalter J, Grigson PS. Ethanol-induced conditioned taste avoidance: reward or aversion? Alcohol Clin Exp Res. 2009; 33:522–530. [PubMed: 19120065]

Liu SW, Lien MH, Fenske NA. The effects of alcohol and drug abuse on the skin. Clin Dermatol. 2010; 28:391–399. [PubMed: 20620755]

McCance-Katz EF, Kosten TR, Jatlow P. Chronic disulfiram treatment effects on intranasal cocaine administration: initial results. Biol Psychiatry. 1998; 43:540–543. [PubMed: 9547934]

National Research Council (U.S.). Committee for the Update of the Guide for the Care and Use of Laboratory Animals., Institute for Laboratory Animal Research (U.S.), National Academies Press (U.S.). Guide for the care and use of laboratory animals. 8. Washington, DC: National Academies Press; 2011.

Negus SS. Effects of punishment on choice between cocaine and food in rhesus monkeys. Psychopharmacology (Berl). 2005; 181:244–252. [PubMed: 15856185]

Nesil T, Kanit L, Collins AC, Pogun S. Individual differences in oral nicotine intake in rats. Neuropharmacology. 2011; 61(1–2):189–201. [PubMed: 21504750]

Nixon K, McClain JA. Adolescence as a critical window for developing an alcohol use disorder: current findings in neuroscience. Curr Opin Psychiatry. 2010; 23:227–232. [PubMed: 20224404]

O'Dell LE, Bruijnzeel AW, Smith RT, Parsons LH, Merves ML, Goldberger BA, et al. Diminished nicotine withdrawal in adolescent rats: implications for vulnerability to addiction. Psychopharmacology (Berl). 2006; 186:612–619. [PubMed: 16598454]

O'Dell LE, Torres OV, Natividad LA, Tejeda HA. Adolescent nicotine exposure produces less affective measures of withdrawal relative to adult nicotine exposure in male rats. Neurotoxicol Teratol. 2007; 29:17–22. [PubMed: 17184972]

Philpot RM, Badanich KA, Kirstein CL. Place conditioning: age-related changes in the rewarding and aversive effects of alcohol. Alcohol Clin Exp Res. 2003; 27:593–599. [PubMed: 12711921]

Riley AL. The paradox of drug taking: the role of the aversive effects of drugs. Physiol Behav. 2011; 103:69–78. [PubMed: 21118698]

Schramm-Sapyta NL, Morris RW, Kuhn CM. Adolescent rats are protected from the conditioned aversive properties of cocaine and lithium chloride. Pharmacol Biochem Behav. 2006; 84:344–352. [PubMed: 16815539]

Schramm-Sapyta NL, Cha YM, Chaudhry S, Wilson WA, Swartzwelder HS, Kuhn CM. Differential anxiogenic, aversive, and locomotor effects of THC in adolescent and adult rats. Psychopharmacology (Berl). 2007; 191:867–877. [PubMed: 17211649]

Schramm-Sapyta NL, Cauley MC, Stangl DK, Glowacz S, Stepp KA, Levin ED, et al. Role of individual and developmental differences in voluntary cocaine intake in rats. Psychopharmacology (Berl). 2011; 215:493–504. [PubMed: 21347641]

Shabani S, McKinnon CS, Reed C, Cunningham CL, Phillips TJ. Sensitivity to rewarding or aversive effects of methamphetamine determines methamphetamine intake. Genes Brain Behav. 2011; 10:625–636. [PubMed: 21554535]

Shram MJ, Funk D, Li Z, Le AD. Periadolescent and adult rats respond differently in tests measuring the rewarding and aversive effects of nicotine. Psychopharmacology (Berl). 2006; 186:201–208. [PubMed: 16586088]

Spear, LP. The behavioral neuroscience of adolescence. 1. NY, USA: W. W. Norton; 2009.

Strolin-Benedetti M, Baltes EL. Drug metabolism and disposition in children. Fundam Clin Pharmacol. 2003; 17:281–299. [PubMed: 12803568]

Torres OV, Tejeda HA, Natividad LA, O'Dell LE. Enhanced vulnerability to the rewarding effects of nicotine during the adolescent period of development. Pharmacol Biochem Behav. 2008; 90:658–663. [PubMed: 18571223]

Vastola BJ, Douglas LA, Varlinskaya EI, Spear LP. Nicotine-induced conditioned place preference in adolescent and adult rats. Physiol Behav. 2002; 77:107–114. [PubMed: 12213508]

Vetter-O'Hagen C, Varlinskaya E, Spear L. Sex differences in ethanol intake and sensitivity to aversive effects during adolescence and adulthood. Alcohol Alcohol. 2009; 44:547–554. [PubMed: 19767625]

Weisshaar E, Grull V, Konig A, Schweinfurth D, Diepgen TL, Eckart WU. The symptom of itch in medical history: highlights through the centuries. Int J Dermatol. 2009; 48:1385–1394. [PubMed: 20415680]

Wilmouth CE, Spear LP. Adolescent and adult rats' aversion to flavors previously paired with nicotine. Ann N Y Acad Sci. 2004; 1021:462–464. [PubMed: 15251930]

Woolverton WL, Freeman KB, Myerson J, Green L. Suppression of cocaine self-administration in monkeys: effects of delayed punishment. Psychopharmacology (Berl). 2012; 220:509–517. [PubMed: 21956240]

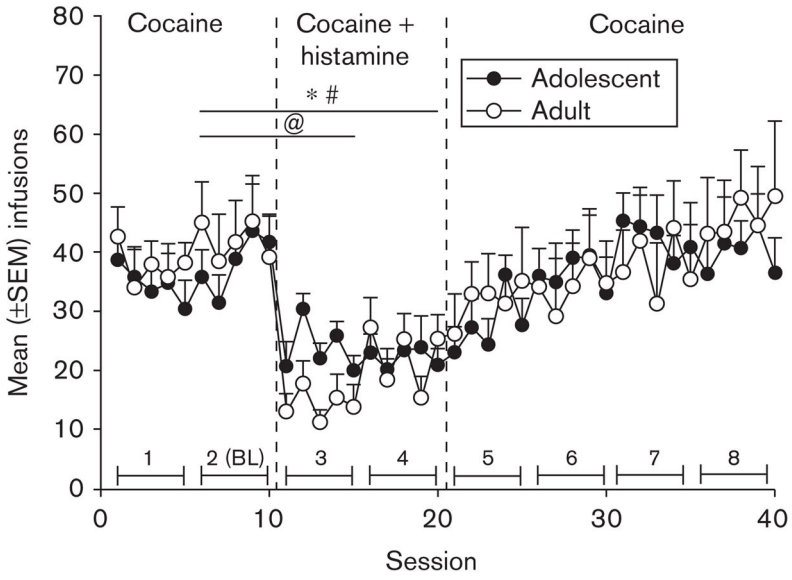

Fig. 1.

Mean infusions self-administered by adolescent and adult rats. Numbered line segments directly above the horizontal axis illustrate blocks of five-session infusion averages. Blocks 1 and 2 constituted the prehistamine phase, blocks 3 and 4 the histamine phase, and blocks 5–8 the posthistamine phase. Block 2 served as the baseline reference measure (BL) of cocaine self-administration before histamine exposure. @, significant difference from baseline (BL, block 2) for the adult group during block 3 ($P < 0.05$); #, significant difference from baseline (BL, block 2) for the adult group during block 4 ($P < 0.05$); *, significant difference from baseline (BL, block 2) for the adolescent group during block 4 ($P < 0.05$).

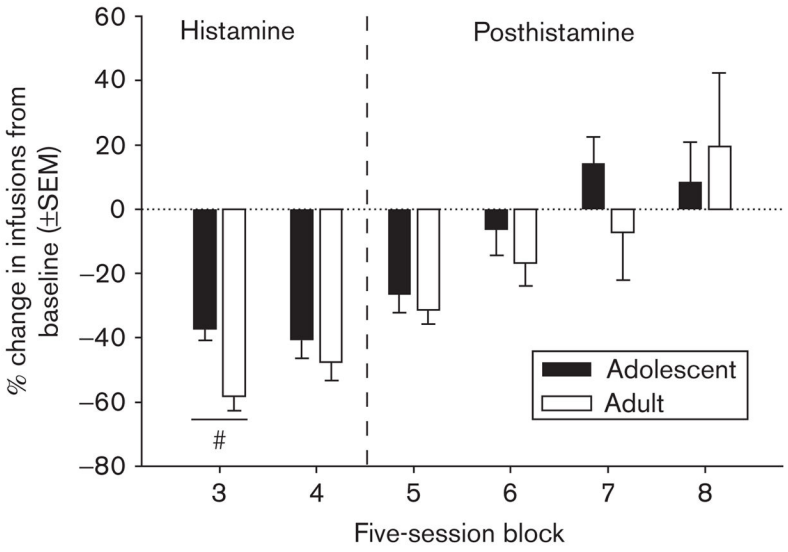

Fig. 2.

Percentage change of infusions self-administered by adult and adolescent rats averaged into 5-day blocks compared with a 5-day baseline average. #, age differences in percentage age change of infusions self-administered between the groups compared with baseline during the histamine phase ($P < 0.05$).