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ORIGINAL INVESTIGATION

# Long-term citalopram maintenance in mice: selective reduction of alcohol-heightened aggression

**Elizabeth E. Caldwell · Klaus A. Miczek**

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**Abstract**
*Background* Selective serotonin reuptake inhibitors (SSRIs) alleviate many affective disturbances in human clinical populations and are used in animal models to study the influence of serotonin (5-HT) on aggressive behavior and impulsivity.
*Objective* We hypothesized that long-term SSRI treatment may reduce aggressive behavior escalated by alcohol consumption in mice. Therefore, aggression was tested in male CFW mice to determine whether repeated citalopram (CIT) administration reduces alcohol-heightened aggression.
*Materials and methods* Resident male mice self-administered alcohol by performing an operant response on a panel placed in their home cage that delivered a 6% alcohol solution. Mice repeatedly confronted an intruder 15 min after self-administration of either 1 g/kg alcohol (EtOH) or water ($H_2O$). Aggressive behaviors were higher in most mice when tests occurred after EtOH intake relative to $H_2O$. Once baseline aggression was established, animals were injected (i.p.) twice daily with 10 mg/kg CIT or saline (SAL) for 32 days. Every 4 days throughout the CIT treatment period, aggressive encounters occurred 6 h after CIT injections, with testing conditions alternating between EtOH and $H_2O$ intake.
*Results* Aggression was only modestly affected by CIT in the first 2 weeks of treatment. However, by day 17 of CIT treatment, alcohol-heightened aggressive behavior was abolished, while baseline aggression remained stable. These data lend support for the role of the 5-HT transporter in the control of alcohol-related aggressive behavior, and the time course of effects suggests that a change in density of $5HT_{1A}$ autoreceptors is necessary before antidepressant drugs produce beneficial outcomes.

**Keywords** Alcohol · Aggression · Serotonin · Antidepressant · Self-administration · Transporter

E. E. Caldwell · K. A. Miczek
Department of Psychology, Tufts University,
Medford, MA 02155, USA

K. A. Miczek (✉)
Departments of Psychiatry, Pharmacology and Experimental Therapeutics, and Neuroscience, Tufts University,
Boston, MA 02118, USA
e-mail: Klaus.Miczek@tufts.edu

Alcohol can increase aggression in some individuals (Bushman and Cooper 1990) especially in individuals with a propensity for impulsive aggressive behavior. According to the 2000 World Report on Violence and Health, more than half of all violent crimes, including assaults, homicides, and rapes, are committed while under the influence of alcohol (Krug et al. 2002), and injuries due to interpersonal violence tend to occur in close proximity to places where alcohol is sold (Gruenewald et al. 2006). Alcohol heightens aggressive behavior in the laboratory for both human and non-human subjects (Parker and Auerhahn 1998; Miczek et al. 2002; see Miczek et al. 2004b). However, most of the time, alcohol consumption does not result in violence, but rather is considered a pleasurable activity that facilitates social interactions, while alcohol-related violence occurs in a small minority of the population (Brady et al. 1998; Cloninger 1987; Linnoila et al. 1983). Preclinical research shows a similar population trend, with a small proportion of rodents (between 15 and 30%) consistently exhibiting escalated attack behavior after alcohol intake (Fish et al. 2001; Miczek et al. 1992, 1998; van Erp and Miczek 1997). It has been hypothesized that a preexisting genetic vulnerability predisposes an individual to drink and to engage in violence as a function of certain

environmental influences (Higley and Bennett 1999; Higley et al. 1996; Meyer-Lindenberg et al. 2006).

Several studies link disorders of the serotonergic system to aggression (Olivier et al. 1995; Popova 2006; Summers et al. 2005; van der Vegt et al. 2003a, b; Linnoila and Virkkunen 1992), and heightened alcohol responsivity (Badawy et al. 1995). Historically, a negative correlation between the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid and impulsive aggressive behavior and risk-taking behavior has been reported in human (Brown et al. 1979, 1982; Linnoila et al. 1983) and non-human primate populations (Fairbanks et al. 2001; Higley et al. 1992; Mehlman et al. 1994). Further evidence identifies regulatory polymorphisms in tryptophan hydroxylase, 5-HT transporter (5-HTT), and monoamine oxidase A promoters in humans (Beitchman et al. 2006; Brunner et al. 1993; Caspi et al. 2002; Haberstick et al. 2006; Hennig et al. 2005; Manuck et al. 2000; Verona et al. 2006) and primates (Barr et al. 2004; Wendland et al. 2006), which are related to violent and impulsive behaviors and, in some cases, also to alcohol consumption (see Wrase et al. 2006).

Serotonergic tone in frontal cortex is thought to be important, specifically for the inhibition of impulsive aggressive behavior, and many treatments aimed at alleviating aggressive behavior in psychiatric patients have targeted serotonergic neurons, especially the transporter molecules (Barkan et al. 2006; Blader 2006; see Bond 2005; Miczek et al. 2002; Reist et al. 2003). Aggressive behavior is reduced after acute systemic administration of direct and indirect serotonergic agonists, particularly the full and partial $5HT_{1B}$ receptor agonists, CP94,253, anpirtoline, zolmitriptan, and eltoprazine (de Boer et al. 1999; Fish et al. 1999; De Almeida et al. 2001, 2006; see Miczek et al. 2004a; Bannai et al. 2007). Treatment with SSRIs has been shown to reduce aggression in patients with borderline personality disorder (New et al. 2004). Citalopram, one of the most selective of the SSRIs, reduced impulsive aggression in clinical and preclinical studies (Reist et al. 2003; Peremans et al. 2005).

Although SSRIs have been found to reduce aggressive behavior in rodents (Delville et al. 1996; Ferris et al. 1997; Pinna et al. 2003), results have been variable. SSRIs differentially affect aggressive behavior in juvenile compared to adult hamsters (Taravosh-Lahn et al. 2006), and the specific aggression-reducing effects of CIT and escitalopram in isolated mice has been less promising (Sanchez et al. 2003). The present experiment is designed to address whether long-term SSRI maintenance, mimicking the clinical regimen, may reduce alcohol-heightened aggressive behavior in mice. To accomplish this objective, chronic daily CIT injections were implemented to increase serotonergic tone in experienced resident male mice. Aggressive behavior was examined after oral self-administration of alcohol during periodic confrontations with intruder males.

## Materials and methods

### Subjects

Adult male CFW mice (Charles River Laboratories, Wilmington, MA, USA), approximately 60 days old and weighing between 20 and 25 g upon arrival, were used as residents ($n$=31) in the present experiment. All resident mice were housed in clear polycarbonate cages (29×19×13 cm) with female conspecifics throughout the experiment. In addition, stimulus mice serving as intruder animals consisted of CFW males, housed six to eight mice per cage in large polycarbonate cages (48×27×17 cm). Mice were housed in a temperature- and humidity-controlled vivarium, maintained at 21–23°C and 30–40% humidity, on a 12:12-h reversed light photocycle (lights off 0600 hours/lights on 1800 hours). All procedures were conducted following strict adherence to the Guide for the Care and Use of Laboratory Animals (National Research Council 1996), and all experimental protocols were approved by the Animal Care and Use Committee at Tufts University.

### Drugs

Citalopram hydrobromide (1-[3(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrobromide) was obtained from Forest Laboratories and dissolved in 0.9% SAL to equal a 1mg/ml solution. Injection volumes were 1 ml/100 g body weight. EtOH solutions (6%w/v) consisted of 95% EtOH diluted with tap $H_2O$.

### Experimental procedures

#### *Alcohol self-administration procedure*

To ensure reliable EtOH self-administration in resident male mice, all animals were restricted to 3 h of access to $H_2O$ each day. After 21 h of $H_2O$ restriction, an aluminum panel was inserted into the home cage, which contained two nose-poke holes with fluid receptacles on the left and right sides of the panel, one of which was designated active and one inactive, with a light illuminated over the active hole and a houselight located on the center of the panel (Miczek and de Almeida 2001). Upon emitting an operant nose poke response (FR 5 schedule) into the active hole (right or left side, counterbalanced), a pump delivered 0.05 ml of fluid into the receptacle located on the panel. Each day, animals self-administered EtOH in increasing concentrations using a modified sucrose-fading technique (Samson 1986) wherein animals initially drank a 10% sucrose-sweetened fluid, after which, EtOH was gradually added to the fluid in 1%

increments while sucrose was gradually faded out until mice self-administered 6% EtOH in $H_2O$. Once sucrose fading was completed, resident mice self-administered 1 g/kg EtOH in their home cages on a daily basis (3–4 days per week), usually within 2–3 min per trial (2.65±0.20, mean±SEM).

*Resident–intruder confrontations*

*Baseline aggressive behavior* After 3 weeks of cohabitation with a female, male resident mice were screened for aggressive behavior during confrontations with an intruder (Miczek and O'Donnell 1978). The screening procedure entailed removal of the female and any pups from the home cage, after which, an intruder male was placed into the home cage. Fighting behavior was observed for 5 min after the first biting attack, or the interaction was terminated after 5 min if no attack occurred. Aggression testing procedures were repeated using the same intruder for each resident every other day, 3 days per week, until aggressive behavior reached stable levels, defined by three consecutive interactions in which attack bite counts were within 15% of the animals' individual average. Stable aggressive behavior was evident by most residents after seven to ten confrontations, and mice demonstrated an average of 22±8 bites per session.

*Alcohol-heightened aggressive behavior* Once stable aggressive behavior was reached, animals were tested for EtOH-heightened aggressive behavior during resident–intruder confrontations, which took place exactly 15 min after each animal reached completion of 1 g/kg EtOH in the self-administration session. Twice per week, animals were examined for aggressive behavior, with test conditions alternating between EtOH and $H_2O$ drinking (in an equal volume, 1.69 ml fluid/100 g body weight). Three determinations of each resident's attack bites directed toward intruders, under both EtOH and $H_2O$ conditions, were obtained, and alcohol-heightened aggressive behavior was calculated from these measurements.

*Chronic treatment with citalopram*

After baseline aggressive behavior was determined under both EtOH and $H_2O$ drinking conditions, animals were treated twice daily with 10 mg/kg (s.c.) CIT ($n$=14) or SAL ($n$=17) in a volume of 1 ml/100 g body weight. This dose was chosen based on reports in mice of anti-immobility effects in the forced swim and tail-suspension tests, which revealed 10 mg/kg as a consistently effective dose (Cryan and Mombereau 2004; Dziedzicka-Wasylewska et al. 2006; Perrault et al. 1992), and based on the knowledge that 10 mg/kg CIT is able to achieve steady-state plasma levels in rodents that correspond to clinically effective doses in humans (Kugelberg et al. 2003). Daily injections were administered between the hours of 0800 and 0930 hours and between 1700 and 1850 hours. Twice daily CIT treatment was repeated for 32 days. As with baseline aggression testing, tests for aggressive behavior were conducted twice a week after drinking either EtOH or $H_2O$. Every test for aggressive behavior was conducted 5–7 h after that morning's injection. This post-injection interval was chosen to obtain behavioral measurements at the drug's average elimination half-life (5 h) and to avoid testing during peak plasma levels of CIT (i.e., 30 min, as observed at comparable doses in the rat; Cremers et al. 2000).

*Aggressive behavior after an acute citalopram injection*

After 1 month of chronic CIT or SAL treatment, animals were tested once for alcohol-heightened aggression 30 min after an injection of 10 mg/kg CIT and once 30 min after a SAL injection. These tests were conducted on the last 2 days of repeated CIT (or SAL) treatment to be used as a comparison between aggression tests conducted 4–6 h post-injection to those conducted 30 min post-injection in chronically treated animals. The rationale for these last two tests is to determine whether aggressive behavior is differentially affected at a post-injection time point which represents peak plasma levels of the drug in comparison to behavior observed during chronic treatment at the longer post-injection intervals used in the present experiment.

*Blood alcohol content determination*

On the last day of the experiment, 15 min after self-administration of 1 g/kg EtOH, blood was collected from mice via intraorbital sinus puncture under isoflurane anesthesia. Blood samples were prepared using an ethanol assay, NAD-ADH reagent (Diagnostic Chemicals, Canada), and determined via UV/VIS spectrophotometer.

Data analyses

Aggressive and non-aggressive behaviors were measured by a trained experimenter during observational analyses of videotaped interactions. The experimenter was trained and practiced analysis techniques until inter-rater and self-reliability scores for all behaviors reached 90% reliability (average inter- and intra-rater reliability scores were 93 and 94%, respectively). Interactions were scored using the Noldus Observer software package. The Observer automatically scored counts, durations, and latencies of every behavior. As previously defined and illustrated (Miczek and O'Donnell 1978), aggressive behaviors included bites, threats, pursuits, and tail rattles. Bites were operationally

defined as any contact with the teeth directed by the resident toward the intruder. A threat was defined when the resident mouse directed a sideways posture toward the intruder, regardless of whether the threat resulted in a bite or not. Pursuits were defined when a resident chased an intruder with the intruder actively fleeing from the resident.

Non-aggressive behaviors included locomotion, rearing, grooming, and social contact with the intruder. Locomotion was measured as any movement of the resident mouse not otherwise specified (included walking, digging, or jumping and flipping against the cage top). Rearing was defined when the two front paws were elevated off the floor. Grooming was defined when the resident engaged in autogrooming, cleaning any part of its body with the forepaws, or scratching the body with the hindpaws. Social contact was measured when the resident made nasal contact with the body of the intruder.

Data were analyzed using SPSS software for the behavioral sciences. One-way analysis of variance (ANOVA) was used to examine baseline differences in aggressive and non-aggressive behaviors for testing that occurred after either EtOH or $H_2O$ drinking. A mixed design, repeated measures ANOVA was performed to analyze the effect of chronic CIT treatment on aggressive behavior under both $H_2O$ and EtOH conditions from pre-experimental baseline through the last day of CIT treatment. The within-subjects factor, *week*, consisted of five levels, baseline, and 4 weeks of drug treatment. The between subjects factor, *drug*, compared SAL and CIT treated subjects. Levine's test for equality of variance and Mauchly's test of sphericity were used, and, where appropriate, corrections were applied. Mice demonstrating substantially augmented attack behavior after drinking EtOH, in excess of two standard deviations of baseline, were designated alcohol-heightened aggressors (AHA). This determination represents a statistical outlier criterion (Barnett and Lewis 1984) previously shown to distinguish animals that reliably demonstrate alcohol-heightened aggressive behavior from those that do not (Miczek et al. 1998). Those that did not evidence the same degree of heightened aggression due to EtOH were designated alcohol non-heightened aggressors (ANA).

## Results

### Alcohol drinking

All mice quickly consumed (within 2.27±0.33 min) 1 mg/kg EtOH 15 min before aggression testing. BAC was determined for a sample ($n$=18) of mice which was measured 15 min after consumption of 1 g/kg EtOH. Mean BAC for the sample was 71.7±1.9 mg/dl, and no differences were found between CIT and SAL conditions for BAC determination.

### Alcohol-heightened aggressive behavior

Resident mice were screened for aggressive behavior repeatedly until stable baseline levels were reached, defined as ≤15% variability between three consecutive agonistic encounters. Once fighting experience was established, each resident male directed an average of 16.3 attacks (±1.3) toward an intruder. Fighting conditions alternated between EtOH and water self-administration. Three determinations were conducted assessing aggression after both EtOH and $H_2O$ consumption, and EtOH drinking heightened attack behavior by 36%. The difference in fighting behavior after EtOH vs $H_2O$ consumption was statistically significant [$t(30)=7.871$, $p<0.001$]. Fourteen mice (45%) demonstrated alcohol-heightened aggressive behavior (mean attacks=26.28±2.27) in excess of two standard deviations above baseline (mean attacks=12.94±1.59) and were therefore designated AHAs. Preliminary analyses showed that the 14 mice which met the statistical criterion for AHA were not different from ANA mice in their response to CIT. Thus, AHA and ANA mice were analyzed together as one sample.

### Effect of CIT on alcohol-heightened aggressive behavior

Repeated daily treatment with CIT significantly reduced baseline aggressive behavior, and after 2 weeks of chronic treatment, CIT completely eliminated alcohol-heightened aggressive behavior. A mixed design repeated measures ANOVA revealed a main effect of week [$F(3,89)=7.149$, $p<0.001$], a main effect of drug [$F(1,29)=8.175$, $p<0.01$], and a significant interaction of week × drug [$F(3,89)=2.822$, $p<0.05$] on total aggression (defined as the sum frequency of bites, threats, pursuits, and tail rattles) after drinking EtOH. The Holm–Sidak method for pairwise multiple comparisons confirmed that CIT significantly decreased aggressive behavior during weeks 3, 4, and 5 compared to baseline (all $p<0.05$), while the SAL group demonstrated no significant change over the 5 weeks of treatment. Importantly, aggression was significantly different between CIT vs SAL groups for EtOH-related aggression week 3 [$t(29)=3.167$, $p<0.01$] and week 4 [$t(22)=2.971$, $p<0.01$], but not weeks 1 and 2 of chronic drug treatment, which demonstrates that the effect of CIT on alcohol-related aggression requires at least 14 days of repeated daily injections (see Fig. 1).

A second ANOVA revealed a main effect of week [$F(4,116)=6.062$, $p<0.001$] and a main effect of drug [$F(1,29)=5.127$, $p<0.05$] on total aggression after drinking $H_2O$. The interaction between drug × week on total aggression was not significant. Figure 1 demonstrates that

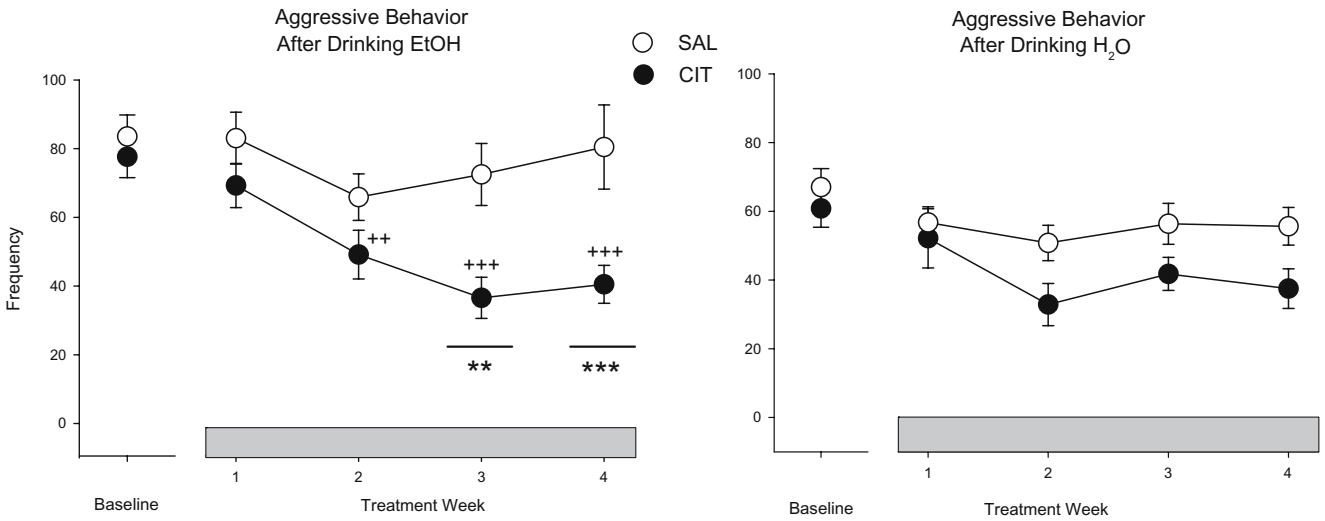


**Fig. 1** Effects of repeated, twice daily (10 mg/kg) CIT injections on aggressive behavior in mice after drinking either EtOH or $H_2O$. Frequency of aggressive acts (defined as sum of attack bites, threats, pursuits, and tail rattles)±SEM. *Plus symbols* indicate statistical significance of behavior relative to baseline (++$p$<0.01; +++$p$<0.001). *Asterisks* indicate a significant effect of CIT compared to SAL (**$p$<0.01; ***$p$<0.001). $n$=14 and 17

the effect of CIT on baseline ($H_2O$) aggression emerged early and remained stable throughout the remaining 3 weeks.

Analyses of attack behaviors alone revealed that CIT significantly reduced the number of attack bites. A main effect of drug [$F(1,29)=5.347$, $p<0.05$] and a main effect of week [$F(4,116)=11.401$, $p<0.001$] was found for attack frequency after drinking EtOH. Although the interaction between CIT × week was not significant, the overall effect of CIT on attacks was clearly more pronounced during the last 2 weeks of treatment (see Fig. 2). In fact, analyses of alcohol-heightened aggressive behaviors for CIT and SAL groups during each week of treatment showed that the heightening effect of EtOH on aggressive behavior was maintained throughout the treatment period for SAL animals (all $p<0.01$), but disappeared in CIT-treated animals after the second week of treatment. Attack bite frequency measured after drinking $H_2O$ did not differ between CIT and SAL mice.

## Effect of CIT on non-aggressive behaviors

A mixed design, repeated measures ANOVA on each non-aggressive behavior measured during testing (both EtOH and $H_2O$ drinking conditions) revealed no significant differences based on drug or week for all behaviors including social contact, grooming, and rearing. A main effect of week emerged for locomotor behavior after drinking EtOH [$F(3,116)=5.692$, $p<0.01$], but had neither a main effect of drug nor interaction of drug × week. As illustrated in the Table 1, both CIT and SAL groups showed an equally substantial decline in locomotion during the last testing session after drinking EtOH.

## Effect of an acute CIT injection on alcohol-related aggression

A subgroup of animals ($n$=26) was tested once for alcohol-induced aggression 30 min after an injection of 10 mg/kg CIT and, counterbalanced on a separate day, 30 min after a

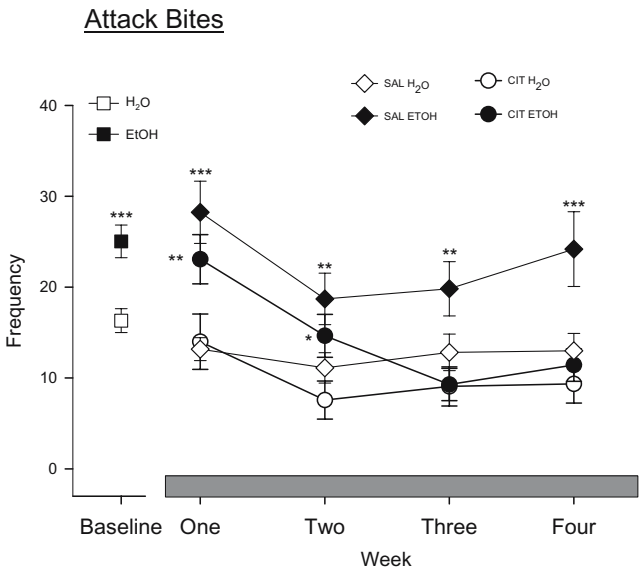


**Fig. 2** Frequency of attack bites at baseline and during chronic CIT treatment. A significant effect of drug was found ($p<0.05$). The aggression reducing effect of CIT was more pronounced during weeks 3 and 4 where attacks after drinking EtOH were significantly ($p<0.01$) lower in CIT (*filled circles*) than SAL-treated animals (*filled diamonds*). Alcohol-heightened attack behavior was eliminated after 2 weeks of CIT treatment, yet remained elevated in SAL-treated mice. *Asterisks* indicate a significant difference between aggression after EtOH relative to $H_2O$ ($p<0.001$). $n$=14 and 17

**Table 1** Substantial decline in locomotion during the last testing session after drinking EtOH

| | | | Baseline | Week 1 | Week 2 | Week 3 | Week 4 |
|---|---|---|---|---|---|---|---|
| Social contact | $H_2O$ | SAL | 4.0±1.6 | 5.3±2.6 | 2.5±0.9 | 9.2±3.9 | 3.0±1.3 |
| | | CIT | 3.0±1.0 | 4.0±2.5 | 5.3±4.6 | 4.9±3.8 | 3.6±1.7 |
| | EtOH | SAL | 4.8±2.1 | 7.9±3.3 | 3.8±1.3 | 8.7±3.4 | 1.4±1.4 |
| | | CIT | 4.6±2.1 | 2.7±2.0 | 6.9±4.7 | 10.4±5.7 | 1.3±1.7 |
| Locomotion | $H_2O$ | SAL | 110.9±4.8 | 104.3±5.8 | 115.1±8.2 | 103.5±6.1 | 112.4±7.1 |
| | | CIT | 114.8±4.2 | 115.1±7.7 | 117.7±10.5 | 103.8±10.0 | 113.8±6.7 |
| | EtOH | SAL | 113.5±5.2 | 118.6±6.0 | 119.5±9.1 | 118.1±5.8 | 81.4±10.3* |
| | | CIT | 115.0±4.4 | 90.6±13.7 | 114.9±9.4 | 102.7±10.3 | 88.9±7.2* |
| Rearing | $H_2O$ | SAL | 67.5±7.6 | 46.8±8.0 | 55.6±8.9 | 65.0±10.6 | 61.7±10.6 |
| | | CIT | 62.1±5.1 | 56.9±9.9 | 57.0±11.7 | 46.7±9.9 | 45.8±9.1 |
| | EtOH | SAL | 53.4±5.3 | 45.9±6.0 | 42.3±6.6 | 39.2±7.1 | 51.4±8.6 |
| | | CIT | 53.4±8.1 | 39.7±8.0 | 43.4±11.6 | 43.3±9.6 | 38.8±9.5 |
| Grooming | $H_2O$ | SAL | 20.7±1.7 | 25.6±5.7 | 18.2±6.1 | 19.4±3.9 | 13.2±3.5 |
| | | CIT | 17.7±3.4 | 20.2±7.4 | 13.0±5.1 | 12.9±2.8 | 17.2±3.6 |
| | EtOH | SAL | 26.4±2.8 | 26.6±6.8 | 20.5±4.3 | 16.6±3.3 | 18.4±5.0 |
| | | CIT | 20.0±4.2 | 22.7±6.6 | 21.7±5.6 | 18.1±5.1 | 17.7±5.1 |

*Significantly different from baseline ($p<0.01$)

SAL injection. For animals maintained on repeated daily SAL injections, one injection of CIT resulted in significantly lower levels of attack bites compared to a single injection of SAL. An ANOVA was performed comparing the between-subjects factor treatment group, which refers to chronically maintained CIT vs SAL mice, and the within-subjects factor drug, either 0 (SAL) or 10 mg/kg CIT. A main effect of drug was detected [$F(1,24)=20.107$, $p<0.001$], and an interaction between treatment group × drug was found on attack bites [$F(1,24)=8.018$, $p<0.01$]. Holm–Sidak post hoc comparisons confirmed that CIT resulted in significantly lower attack bites compared to SAL injections [$t(25)=5.898$, $p<0.001$] and showed that animals chronically maintained on SAL showed a significant reduction in aggressive behavior 30 min after CIT injections, but animals with a history of chronic CIT treatment did not evidence the same reduction in aggressive behavior (Fig. 3). Similarly, CIT injections reduced individual measurements of threats and tail rattles (all $p<0.01$). Mean threat frequency (±SEM) for SAL and CIT was 13.8±1.4 and 8.3±0.9, respectively. Mean tail rattle frequency (±SEM) for SAL and CIT was 12.3±1.4 and 4.7±0.8, respectively. A main effect was found for locomotor behavior 30 min post-injection. Interestingly, an acute CIT injection resulted in significantly higher rates of locomotor behavior than a SAL injection [$t(25)=2.953$, $p<0.001$] for

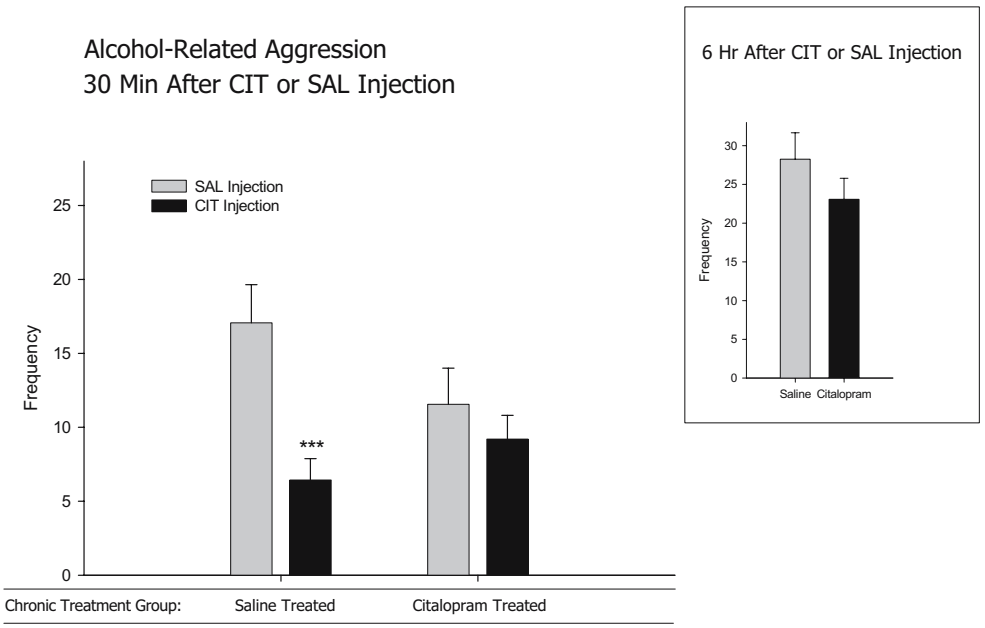


**Fig. 3** Aggressive behavior 30 min after an acute injection of CIT, 15 min after drinking alcohol. Only SAL-maintained animals show a pronounced reduction in aggressive behavior after an acute injection of CIT. Compare to day 1 of chronic treatment (*inset*) wherein no differences emerged between CIT and SAL when interactions occurred 6 h post-injection. Therefore, a single injection of CIT reduces alcohol-related aggression, but this reduction is only apparent during elevated plasma levels of the drug. $n=10$ and 16

both treatment groups, with no significant interaction between treatment group × drug.

## Discussion

The present experiments represent the first investigation of long-term antidepressant treatment on alcohol-heightened aggression in rodents. The purpose of conducting tests of aggressive behavior at a time divorced from initial rapid drug effects is to mimic human treatment strategies in an effort to find enduring, rather than transient, changes in behavior. Until now, most behavioral studies have examined acute actions of antidepressants (Crowley et al. 2005; de Boer et al. 1999, 2000; Sanchez et al. 2003). Those examining long-term antidepressant treatment have utilized depression- and anxiety-like behavioral protocols such as forced swim, tail suspension, open field, novelty-suppressed feeding, and ultrasonic distress vocalizations (Connor et al. 2000; Santarelli et al. 2003; Fish et al. 2004), research which consistently shows that antidepressants dose-dependently reduce anxiety- and depression-like behaviors. Some research on rodent aggression has shown that acute administration of SSRIs lengthens attack latency (Sanchez et al. 2003) and has been found to dose-dependently reduce aggressive behaviors (de Boer et al. 1999, 2000; Taravosh-Lahn et al. 2006), but antidepressants have also produced variable effects on attack frequency in rodents (Rilke et al. 2001). A series of studies reported that long-term SSRI treatment affects establishment of dominance hierarchies and enhances agonistic behavior and social competence in colony housed rodents (Mitchell 2005; Mitchell and Redfern 1997; Mitchell et al. 1991), yet none have examined changes in alcohol-related aggressive, social, and locomotor behavior after repeated daily SSRI treatment. The present results represent an encouraging development in the search for therapeutic strategies aimed at alleviating chronic alcohol-related violence in humans.

Chronic treatment with SSRI, but not other types of antidepressants, modulate the uptake process of 5-HT, reduces SERT binding in the CA3 region of the hippocampus (Benmansour et al. 1999), and desensitizes the 5HTT (Piñeyro et al. 1994). Of all the SSRI antidepressants, CIT and ESC are the most selective for blocking 5HTT. These results therefore demonstrate that the 5HTT is important for the regulation of aggressive behavior and suggest that blockade of the transporter is a useful strategy for reducing strong aggressive tendencies in individuals.

Because alcohol-related violence in humans is thought to be an enduring and maladaptive trait, it is important not only to distinguish between alcohol-heightened (or escalated) and species-typical forms of aggressive behavior but also to distinguish between both short- and long-term consequences of altered monoamine levels. Citalopram increases 5-HT levels immediately, reaching peak plasma concentration in approximately 30–40 min, and cortical increases in extracellular 5-HT levels are maximally increased 40–60 min post-injection (Cremers et al. 2000). The rationale for conducting a single probe of aggressive behavior 30 min after an acute injection of CIT was to demonstrate that changes in aggressive behavior occur differentially based on whether animals are chronically vs acutely treated with CIT and whether behavior is altered during peak plasma levels of the drug compared to a 6-h post-injection interval. Indeed, CIT reduced aggressive behavior acutely in SAL-maintained animals, suggesting that even transient increases in extracellular 5-HT are effective. Compared to the first day of chronic treatment, when aggression testing occurred 6 h post-injection, the difference between SAL and CIT is far more substantial. Thus, the aggression-reducing effect of acute CIT administration is likely transient in nature, while the more dramatic long-term changes in the reduction of escalated aggression occur after repeated administration.

Chronic citalopram treatment affected baseline (water condition) aggression, an effect which emerged by the second week and persisted throughout the treatment period. However, the reduction in alcohol-heightened aggressive behavior was most impressive. Alcohol-related aggression was reduced by CIT treatment, and although this effect began to emerge during the second week of treatment, the main effect of alcohol on aggressive behavior was completely abolished by the third week of treatment, a time course which is very similar to the temporal effects of antidepressants on depressive symptoms in humans. This also corresponds to the time when autoreceptors are believed to have become desensitized (see Blier and de Montigny 1998; Ceglia et al. 2004). At the same time, these effects correspond to a time when hippocampal neurogenesis is known to be enhanced (Santarelli et al. 2003) and effects are also congruent with the return of suppressed 5-HT firing activity observed in the hippocampus after chronic CIT treatment in rats (Mansari et al. 2005).

Acute treatment with CIT or ESC maximally increases extracellular 5-HT (Ceglia et al. 2004), and prolonged treatment with CIT may not result in significantly higher dialysate 5-HT during a CIT challenge compared to SAL-maintained animals (Auerbach and Hjorth 1995; Hjorth and Auerbach 1999). However, multiple studies do report functional changes in the 5-HT levels and changes in brain serotonin transporter (SERT density and mRNA expression in the raphe) after chronic SSRI antidepressant treatment (Benmansour et al. 1999).

Projections terminating in the prefrontal cortex are thought to be important for the regulation of impulsive aggressive behavior as well as behavioral responses to alcohol (Badawy et al. 1995; Fahlke and Hansen 1999;

Hinkers et al. 2006; see Wrase et al. 2006). Somatodendritic $5HT_{1A}$ autoreceptors located on cell bodies within the raphe are thought to be important for the latency of SSRI effects (Ceglia et al. 2004; De Vry et al. 2004; Santarelli et al. 2003). Serotonin levels depend on raphe neuronal activity, and although antidepressants enhance terminal 5-HT levels immediately, antidepressant efficacy is delayed likely due to the time required for autoreceptor desensitization (Hughes et al. 2007; also see Kalsner 2000).

Whether autoreceptor desensitization accounts for some of the behavioral effects seen here could be determined by incorporating daily administration of $5HT_{1A}$ receptor antagonists (e.g., WAY-100635) in addition to SSRI treatment wherein SSRI effects would be predicted to emerge earlier. de Boer et al. (2000) found that WAY-100635 combined with S-15535 resulted in additive aggression-reducing effects. In addition, WAY-100635 augments the increased extracellular 5-HT in the dialysate due to CIT (Cremers et al. 2000; Hjorth et al. 1997), supporting the supposition that $5\text{-}HT_{1A}$ autoreceptors play a regulatory role in the onset of SSRI treatment effects. Therefore, this strategy could currently be implemented to reduce alcohol-heightened aggression more rapidly.

The clinical translation of the present findings suggests that long-term SSRI treatment may be a useful therapeutic strategy for reducing escalated aggressive behavior due to alcohol consumption.

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