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Clozapine chronically suppresses alcohol drinking in Syrian golden hamsters

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Abstract

Alcohol use disorder is common in patients with schizophrenia and is associated with poor clinical outcomes. Preliminary reports from our group and others suggest that the atypical antipsychotic clozapine may decrease alcohol use in these patients. We have previously shown that clozapine suppresses alcohol consumption for 9 days in Syrian golden hamsters. Here, we assessed the effects of clozapine on alcohol consumption in hamsters over a 27-day period, using a continuous access, 2-bottle (15% alcohol vs. water) protocol. Clozapine (4, 8, or 12 mg/kg/day, injected subcutaneously [s.c.]) dose-dependently suppressed alcohol drinking, while increasing food and water intake, and there was no tolerance within individual groups to this effect of clozapine over time. In a separate experiment, the effects of clozapine on sucrose and water drinking and food intake over a 9-day period were assessed. Clozapine (4, 8, or 12 mg/kg/day s.c.) failed to suppress sucrose (0.09 M), food, or water consumption at any time-point tested. In a related study, assessment of blood alcohol levels in hamsters indicated that blood alcohol levels were maintained within a narrow and moderate range (7–13 mg/dL), levels noted by others to produce physiologic effects in rodents. The ability of clozapine to suppress alcohol drinking in the hamster over an extended period of time without suppressing sucrose, water, or food consumption is consistent with preliminary reports indicating that clozapine limits frequent alcohol use, even producing abstinence in many patients with schizophrenia.

Keywords

Clozapine; Schizophrenia; Alcoholism; Sucrose; Blood alcohol level; Hamster

1. Introduction

More than 30% of patients with schizophrenia have co-occurring alcohol use disorder, a rate threefold higher than in the general population (Drake et al., 1989; Regier et al., 1990). A majority of these patients tend to consume moderate quantities of alcohol on a regular basis,

often without development of physical dependence. Even such moderate alcohol use, however, has been consistently shown to worsen the clinical course of patients with schizophrenia (Alterman et al., 1981; Drake and Mueser, 1996; Gupta et al., 1996; Owen et al., 1996). Treatment options for these comorbid individuals are severely limited and most antipsychotic medications (especially the typical antipsychotic agents) used in these patients have little impact on their alcohol use or may even exacerbate it. We and others, however, have recently noted that patients treated with the atypical antipsychotic clozapine had strikingly higher rates of remission from alcohol abuse, compared to those who were treated with other antipsychotic medications.

To further investigate the ability of clozapine to limit alcohol consumption, our group has assessed the effects of clozapine in the alcohol-preferring Syrian golden hamster (*Mesocricetus auratus*). Unlike rat and mouse models of alcohol dependence, the golden hamster appears to fit the profile of an animal model of moderate alcohol drinking – it tends to drink alcohol at an even pace (2–2.5 g/kg/3 h); it develops moderate blood alcohol levels (BAL, 1–3 mM) (Keung et al., 2000); and it does not exhibit signs of physiological withdrawal following cessation of chronic alcohol drinking (McMillan et al., 1977). In a prior study, using a continuous access, 2-bottle (alcohol vs. water) test paradigm, we showed that relatively low doses of clozapine (2–4 mg/kg/day) administered via daily subcutaneous (s.c.) injection over 9 days suppressed alcohol drinking in this animal (Green et al., 2004). However, a few questions arose from this study. First, does tolerance (e.g., loss of suppression of alcohol drinking by clozapine) develop if clozapine treatment continues beyond 9 days? Second, does clozapine produce a selective decrease in alcohol consumption or a general decrease in consumption of food and water, or other naturally reinforcing solutions such as sucrose? Lastly, do the hamsters have a high enough blood alcohol level, as previously reported by Keung et al. (2000), that would indicate a physiological effect of alcohol in this animal? To address these questions, the current experiments examine the effects of prolonged clozapine treatment on alcohol drinking, the effects of clozapine treatment on sucrose and water drinking, and the blood alcohol levels achieved by free-drinking golden hamsters.

2. Material and methods

2.1. Animals

Adult, male Syrian golden hamsters (*M. auratus*), (100–130 g) were acquired from Harlan Inc. (Indianapolis, IN), maintained on a normal 12 h/12 h light/dark cycle (light off at 7 PM), and individually housed in standard home cages with ad libitum access to food and water. Animals in Experiments 1 and 3 were given continuous access to a bottle of water and a second bottle containing alcohol. Animals in Experiment 2 were given continuous access to a bottle of water and a second bottle containing either sucrose or water. Within each experiment, the positions of the two drinking bottles were rotated on a daily basis to prevent positional preference. A technician, blinded to the experimental conditions, measured fluid intake every 24 h, food intake every 48 h, and body weight every 3–5 days. Measurements took place at the same time each day (between 1 PM and 4 PM). All experiments were carried out in accordance with the National Institutes of Health guide for

the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and were approved by Dartmouth Institutional Animal Care and Use Committee.

2.2. Experiment 1: effects of clozapine treatment on alcohol drinking over 27 days

Thirty-five adult male Syrian golden hamsters were given access to 15% (v/v) alcohol for 24 days prior to randomization into 5 groups ($n = 7$ per group) with similar baseline alcohol intake values (g/kg/day) (baseline alcohol intake was calculated using the last 4 days of the initial 24-day period of access to alcohol). Each group was subsequently treated daily for 27 days with 4 mg/kg clozapine (CLOZ4), 8 mg/kg clozapine (CLOZ8), 12 mg/kg clozapine (CLOZ12), or vehicle (VEH). In those animals receiving more than 4 mg/kg clozapine per day, dosing began at 4 mg/kg on the first day, and on subsequent days, the doses were increased by 4 mg/kg/day up to the targeted values, i.e., 8 or 12 mg/kg. All hamsters continued to receive free access to food, water, and alcohol during the treatment period.

2.3. Experiment 2: effects of clozapine treatment on sucrose, water, and food intake over 9 days

Twenty-eight adult male Syrian golden hamsters were given a water bottle and a 0.09 M sucrose bottle and 28 animals were given two bottles containing water. After 24 days of continuous access to these fluids, each set of 28 animals was divided into 4 groups with similar baseline sucrose or water intake values (g/kg/day), calculated using data from the last 4 days of the initial 24-day period. Each group was subsequently treated daily for 9 days with 4 mg/kg clozapine (CLOZ4), 8 mg/kg clozapine (CLOZ8), 12 mg/kg clozapine (CLOZ12), or vehicle (VEH), as described for Experiment 1.

2.4. Medication preparation & administration

Clozapine solutions were prepared for injection by first dissolving clozapine (Sigma–Aldrich Co.) in 0.5 N acetic acid, then adjusting the volume to the desired clozapine concentration using a vehicle solution (VEH, 0.5 M sodium acetate, pH 5.0). The pH of each drug solution was also adjusted to 5.0 using 5 N NaOH. All drug and vehicle solutions were injected s.c. in volumes of 2 ml/kg body weight. All injections were given 5 h before dark (at 1 PM) to prevent potential acute motor side effects from the drug from interfering with drinking and eating (which normally occur during the dark cycle). Our previous study determined that clozapine given 5 h before dark can substantially reduce alcohol drinking in hamsters during the 24 h following the injection (Green et al., 2004).

2.5. Experiment 3: determination of Blood Alcohol Level (BAL)

To confirm previously reported data indicating that the Syrian golden hamster will ingest alcohol to achieve a moderate BAL, we assessed BALs in 20 drug-free hamsters (Keung et al., 2000). All hamsters were given continuous access to 15% (v/v) alcohol and water in 2 separate bottles for 24 days, as in Experiment 1. After 24 days, hamsters were randomized into 5 groups ($n = 5$ –6 per group) according to baseline alcohol intake values (g/kg). On the final night of alcohol drinking (Day 24), blood samples were collected at 2, 4, 6, 8, and 10 h into the dark cycle from animals in groups 1, 2, 3, 4 and 5, respectively. For blood collection, animals were anesthetized with a combination of ketamine and xylazine and 2–3

ml of blood were collected from each animal directly from the heart. Blood samples were centrifuged (1400 rpm, 5–10 min), and the resulting blood plasma was stored in a -80°C freezer for analysis the following day. Alcohol levels in blood plasma samples were measured using an alcohol oxidase enzyme-based analyzer from Analox Instruments (Model GM7). To control for intra-assay variability, the alcohol level was analyzed in 2–3 aliquots from each plasma volume sample, and the averaged value of these samples was used for data analysis.

2.6. Data analysis

Alcohol intake (g/kg), sucrose intake (g/kg), water intake (ml), food intake (g), and body weight (g) data were analyzed using two-way repeated measures analysis of variance (ANOVA), using time (3 or 4-day blocks) and drug treatment as independent variables. When the analysis indicated that significant differences existed between treatments, post-hoc pairwise comparisons between groups were made using the Tukey adjustment. Post-hoc pairwise comparisons were also made to compare baseline and treatment days using Tukey's HSD tests. Comparison of mean BALs between different time points was made using one-way repeated measure ANOVA. Significance was determined at $p < 0.05$. Data are expressed as mean (M) $\pm$ standard error of the mean (SEM).

3. Results

3.1. Experiment 1

3.1.1. Effects of clozapine on alcohol consumption

3.1.1.1. Alcohol drinking: Two-way repeated measures ANOVA with time and drug treatment as independent variables indicated significant effects of time ($F(9,260) = 22.66$, $p < 0.001$) and treatment group ($F(3,23) = 4.89$, $p < 0.01$) on alcohol consumption (g/kg), as well as a group by time interaction ($F(27,243) = 2.05$, $p < 0.05$) (Fig. 1). Tukey's post-hoc tests indicated that there was no significant difference between groups in alcohol consumption during the baseline period, indicating effective randomization into groups. During the first 6 days of treatment, the clozapine-treated groups (CLOZ4, CLOZ8, CLOZ12) drank less alcohol than the vehicle-treated group (VEH) ($p < 0.05$). During the subsequent 18 treatment days, significant differences were noted only between the group treated with the highest dose (CLOZ12) and VEH. The differences between the VEH group and the CLOZ4 and CLOZ8 groups were not significant during the last 18 treatment days. To assess the trends in mean alcohol intake over time, one-way ANOVA of the alcohol drinking data with time as the independent variable was performed for each individual treatment group. The analysis indicated that alcohol intake stabilized at a level below baseline for all three clozapine-treated groups, once the targeted clozapine doses were reached. This level, once reached, was subsequently maintained throughout the rest of the experiment. Thus, clozapine dose-dependently decreased alcohol consumption, and there was no tolerance within individual groups to this effect of clozapine over time.

3.1.1.2. Water drinking: Two-way repeated measures ANOVA with time and drug treatment as independent variables indicated a significant effect of time ($F(9,260) = 9.54$, $p < 0.001$) on water drinking (ml), but no effect of group nor group by time interaction (Fig.

2). Further analysis comparing water intake during the baseline period to averaged water intake during the 27-day treatment period, using 2-way ANOVA with time (baseline period vs. treatment period) and treatment group (VEH, CLOZ4, CLOZ8, CLOZ12) as independent variables, also indicated an effect of time ($F(1,52) = 13.08, p < 0.001$), but no effect of group nor group by time interaction. However, when data from all clozapine-treated groups were combined and compared against VEH, there was a trend toward a difference between groups ($F(1,25) = 3.92, p < 0.06$) and a significant effect of time ($F(1,52) = 4.83, p < 0.05$), as well as a time by group interaction ($F(1,54) = 4.83, p < 0.05$). Post-hoc tests indicated that clozapine-treated animals drank more water than vehicle-treated animals during the treatment period but not during the baseline period ($t(30) = 3.82, p < 0.001$).

3.1.1.3. Food intake: Because food intake during the baseline period was different between groups, analyses of food intake were performed using data expressed as percentage of baseline. Two-way ANOVA indicated significant effects of time (4-day blocks) ($F(7,208) = 3.87, p < 0.01$) and group ($F(3,23) = 6.90, p < 0.01$) on food intake, but no group by time interaction (Fig. 2). Post-hoc one-way ANOVA of food intake during the treatment period also indicated significant group differences ($F(3,23) = 6.90, p < 0.05$), due to greater increases in food intake in the CLOZ12 group, compared to animals treated with VEH.

3.1.1.4. Body weight: There were significant effects of time ($F(5,135) = 24.35, p < 0.001$) and group ($F(3,23) = 3.02, p = 0.05$) on body weight, but no group by time interaction. Post-hoc Tukey tests indicated that all groups gained body weight during the experiment ($p < 0.05$). However, the change in body weight was less in clozapine-treated groups than in the VEH group ($p < 0.05$) (data not shown).

3.2. Experiment 2

3.2.1. Effects of clozapine on sucrose consumption—Among the 4 treatment groups (VEH, CLOZ4, CLOZ8, CLOZ12) exposed to sucrose, there were no significant differences between groups in sucrose consumption (g/kg) during the baseline period, indicating effective randomization into groups. There was no effect of time or group on sucrose consumption during treatment, and no time by group interaction (data not shown). We also examined sucrose preference (mL sucrose consumed/total mL fluid consumed). There was a significant effect of time ($F(3,72) = 98.7, p < 0.05$) on sucrose preference but no effect of group and no group by time interaction. Tukey's post-hoc tests revealed that sucrose preference was equal between baseline and days 1–3 of the treatment phase, but that preference decreased between days 1–3 and days 4–6 of treatment and again between days 4–6 and days 7–9 of treatment ($p < 0.05$; Fig.). However, because there was no 3 difference between groups, this indicates a decrease in sucrose preference over time but not as a result of clozapine treatment.

3.2.2. Effects of clozapine on water and food consumption—There was a significant effect of time ($F(3,72) = 29.1, p < 0.001$), but no effect of group, on water consumption, and no group by time interaction. Tukey's post-hoc tests revealed a trend toward increased water consumption over time in the vehicle-treated group (Fig. 4). There was no effect of time or group on food consumption, and no time by group interaction.

There was a trend toward decreased food consumption in all clozapine-treated groups in the final three days of treatment, and an increase in food consumption in the vehicle-treated group, but this trend did not reach statistical significance ($p = 0.06$; Fig. 4). There was also an effect of time on body weight ($F(3,144) = 118.32$, $p < 0.001$) but there was no effect of group and no group by time interaction. Tukey's post-hoc tests indicated significant weight gain over time across all groups ($p < 0.05$; data not shown). Thus, clozapine did not alter body weight or water and food consumption.

3.3. Blood alcohol level (BAL)

We measured baseline alcohol intake over 24 h (see Methods), then measured alcohol intake during sequential 2-h periods starting 2 h after the onset of the dark cycle. Blood collection occurred at 5 different time points during the dark cycle (2, 4, 6, 8 and 10 h after dark), in 5 separate groups of hamsters (Table 1). There were no differences in body weight or daily rates of alcohol intake among groups during the 4 days prior to blood collection, indicating that randomization of group assignment was effective. The amount of alcohol consumed during the 2 h prior to blood collection (Group 1: 7–9 PM; Group 2: 9–11 PM; Group 3: 11 PM–1 AM; Group 4: 1–3 AM; Group 5: 3–5 AM) was similar between groups. However, there was a significant difference in BAL measured at different time points ($F(4,21) = 6.47$, $p < 0.01$). Pairwise comparisons between individual groups indicated that BAL tended to be higher during the latter hours of the dark cycle (9 PM vs. 3 AM, $p < 0.05$; 9 PM vs. 5 AM, $p < 0.01$; 11 PM vs. 5 AM, $p < 0.05$; 1 AM vs. 5 AM, $p < 0.05$).

4. Discussion

The current data show that clozapine (4, 8, and 12 mg/kg/day, injected s.c. over 27 days) suppressed alcohol drinking while increasing food and water intake. The suppression of alcohol drinking was dose-dependent, and there was no tolerance within individual groups to this effect of clozapine over time. Moreover, clozapine (4, 8, and 12 mg/kg/day given over 9 days) did not alter consumption of 0.09 M sucrose, water, or food (in the absence of alcohol) at any time-point tested. We also found that hamsters tended to consume alcohol at an even pace throughout the dark cycle (about 1.5 g/kg/hour) and their blood alcohol levels were maintained within a narrow and moderate range (4.4–18.9 mg/dL). Taken together, these data suggest that clozapine may suppress chronic, moderate alcohol drinking, without decreasing consumption of a sweet solution, water, or food. Such data are consistent with preliminary reports indicating that clozapine limits the moderate alcohol use seen in patients with schizophrenia.

In a prior study, we injected clozapine in hamsters 5 h before dark (during the animal's sleeping hours) and found that such treatment decreased alcohol consumption over the next 24 h. In the current study, we followed the same injection procedure. Studies have shown that clozapine and its metabolites are rapidly eliminated (e.g., half-life in blood = 1.5–1.6 h) (Baldessarini et al., 1993), and that the acute side effects of clozapine injection are also short-lived. For example, clozapine is known to decrease food-reinforced behavior only in the first 3 h following administration, but not later (Sun and Lau, 2000). Thus, our rationale for injecting clozapine in the animals 5 h before dark was to limit the drug's potential acute side effects (motor impairment or sedation) to the animals' sleeping period. The fact that

food and water intake increased during clozapine treatment, while alcohol drinking decreased, suggests that a shift in preference for the choice of fluid (water over alcohol) and source of calories (food over alcohol) occurred. Regarding the “selectivity” of clozapine’s action on alcohol drinking, our data show that clozapine treatment did not alter sucrose (0.09 M) consumption. Taken together, these data suggest that clozapine may decrease alcohol consumption, without interfering with normal eating or water drinking or consumption of a mildly reinforcing solution. Future studies should, however, further assess the selectivity of clozapine (for alcohol vs. other reinforcers, such as more concentrated sucrose solutions and other palatable fluids), especially since other currently used medications such as naltrexone and acamprosate have been shown to produce comparable decreases in ethanol and sucrose intake in rodents (Czachowski and Delory, 2009; Sharpe and Samson, 2001; Stromberg et al., 2002).

Several groups have previously assessed the effects of clozapine in rats and mice. The results from these studies are varied, and depend on the length of treatment, as well as on the paradigm used. June et al. (1991), for example, reported increased alcohol drinking in rats administered single doses of clozapine (1–4 mg/kg) in a limited-access paradigm. However, Thrasher et al. (1999) found no changes in alcohol drinking in C57BL/6J mice following a single dose of 1 mg/kg, using a similar limited-access paradigm. Likewise, Ingman and Korpi (2006) found no significant changes in alcohol drinking in alcohol-preferring AA (Alko, Alcohol) rats following a single dose or 5 daily doses of 0.3–5 mg/kg/day, using a limited-access paradigm. Yet Ufer et al. (1999), using a continuous-access paradigm, showed that Sprague–Dawley rats decreased their consumption of a mixed 5% alcohol and saccharin solution during a 9-day period in which the animals ingested clozapine in their diet (approximately 20 mg/kg/day).

The current data are consistent with our previous study in hamsters (Green et al., 2004) and the study by Ufer et al. (1999) in Sprague–Dawley rats, both of which employed continuous-access 2-bottle choice procedures similar to those used here. By contrast, as noted above, investigators who used limited-access paradigms have shown no effect of clozapine on alcohol drinking in alcohol-preferring rats and mice (Ingman and Korpi, 2006; June et al., 1991; Thrasher et al., 1999). Such discrepancies suggest that the outcome of clozapine treatment may depend on the alcohol drinking paradigm employed (Green et al., 2004). Limited-access protocols involve intermittent alcohol deprivation, possibly followed by binge-like drinking behavior (Nowak et al., 1999), whereas continuous-access protocols allow alcohol drinking to occur naturally. The fact that clozapine has been more effective in this study and in studies that used the continuous-access paradigm suggests that clozapine may preferentially target mechanisms involved in the maintenance of alcohol drinking. Further, these data imply that clozapine may suppress maintenance of alcohol drinking in non-dependent animals, since the hamsters are known not to undergo physiological withdrawal.

When judging the therapeutic potential of a medication that may be used to control alcohol drinking, it is important to consider the effects of such a medication over time. Studies of medications such as haloperidol, which does not limit alcohol use in patients with schizophrenia, have demonstrated a loss of suppression of free access alcohol drinking in

rodents 1–2 weeks into treatment. However, we found no tolerance to the effects of clozapine on alcohol drinking in the golden hamster over a 27-day treatment period. This chronic suppression of alcohol drinking by clozapine is consistent with preliminary observations indicating that clozapine treatment in patients with schizophrenia and co-occurring alcohol use disorder is associated with decreased alcohol use and increased abstinence from alcohol in these patients.

We have proposed that clozapine, through its actions on serotonergic and noradrenergic neurons (especially its antagonistic effects on noradrenergic α -2 adrenergic receptors and its ability to chronically elevate norepinephrine in the plasma and brain), coupled with its weak dopamine D2 receptor blocking ability, may tend to have a “normalizing” effect on the dysfunctional mesocorticolimbic system that underlies substance use disorder in these patients (Green et al., 1999). Studies using treatment durations and doses of clozapine similar to those used here have shown that repeated clozapine administration enhances functioning of the mesocorticolimbic dopamine reward circuit. For example, clozapine given over 21 days, with the daily dose adjusted to match a therapeutic dose in humans, is known to increase the release of dopamine in the medial prefrontal cortex (Youngren et al., 1994); to increase self-stimulation in the ventral tegmental area (Gardner and Seeger, 1988); and to produce long-lasting decreases in self-stimulation thresholds in the nucleus accumbens (Gardner and Seeger, 1983).

An alternative explanation for the suppression of alcohol consumption by clozapine is that clozapine may act on the mesocorticolimbic system to decrease the threshold for the pharmacological effects of ethanol. Thus, clozapine may decrease the amount of alcohol that must be consumed for it to be rewarding. In order to address this possibility, we have initiated a series of studies examining the effects of clozapine on operant responding for food, water, sucrose and ethanol in the golden hamster.

In conclusion, while the Syrian golden hamster is not an animal model of schizophrenia per se, on the basis of its moderate alcohol consumption and its response to clozapine, it may be a useful animal in which to assess potential medications for limiting alcohol use in patients with schizophrenia. In light of the current data indicating that clozapine suppresses alcohol drinking while increasing food and water intake in this animal, further research on the mechanism of action of clozapine in the hamster may lead to a new approach in the treatment of patients with co-occurring alcohol use disorder and schizophrenia.

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Fig. 1.

Effects of clozapine treatment on alcohol drinking in hamsters. Prior to randomization into treatment groups, all animals had 24 days of free-choice access to alcohol and water in 2 separate bottles. Baseline alcohol intake was taken as the 4 days (Days -3, -2, -1, and 0) immediately prior to the initiation of treatment. During the Treatment Phase, clozapine (4, 8, or 12 mg/kg) was injected once daily over 27 days (Days 1–27). All doses of clozapine (CLOZ) but not vehicle (VEH) decreased alcohol drinking below baseline. The changes were dose-dependent and relatively stable over time.

Fig. 2.

Effects of clozapine treatment on food and water. All doses of clozapine (CLOZ), but not vehicle (VEH), increased food intake (top) and water intake (bottom), while they decreased alcohol drinking. Clozapine did not alter total daily caloric intake (data not shown). Empty bars: averaged rates during the baseline period. Solid bars: average rates during the treatment period.

Fig. 3.

Effect of clozapine treatment on sucrose preference. Although sucrose preference decreased over time, there was no effect of clozapine treatment on sucrose preference.

Fig. 4. Effects of clozapine treatment on food and water intake. Clozapine failed to alter food intake (top) or water intake (bottom). Clozapine did not alter total daily caloric intake (data not shown). Empty bars: averaged rates during the baseline period. Solid bars: average rates during the treatment period.

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Table 1

Alcohol drinking and corresponding blood alcohol level.

Time of blood collection (hours into the dark)	Group	Body weight (g)	24-h Alcohol intake (g/kg)	2-h Alcohol intake (g/kg)	Mean BAL (mg/dL)	BAL range (mg/dL)
2 (9 PM)	1 (<i>n</i> = 6)	121 ± 6	15.7 ± 1.3	2.8 ± 0.3	6.9 ± 1.0	4.4–10.5
4 (11 PM)	2 (<i>n</i> = 6)	119 ± 5	15.0 ± 1.5	3.1 ± 0.3	8.4 ± 0.8	6.1–10.2
6 (1 AM)	3 (<i>n</i> = 5)	123 ± 2	15.4 ± 1.3	3.0 ± 0.1	7.9 ± 0.6	6.4–9.3
8 (3 AM)	4 (<i>n</i> = 5)	121 ± 1	15.6 ± 1.2	3.3 ± 0.2	11.1 ± 0.3	10.6–12.2
10 (5 AM)	5 (<i>n</i> = 5)	124 ± 4	15.4 ± 1.2	3.1 ± 0.3	13.0 ± 2.3	10.5–18.9