Wheel-running exercise during adolescence does not substantially affect cocaine conditioned place preference in male C57BL/6J mice

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Introduction

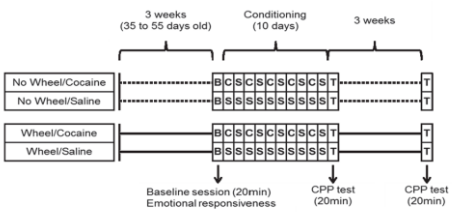
Epidemiological studies suggest that physical exercise could have preventive properties against drugs of abuse vulnerability (Lisha and Sussman, 2010).

Animal research showed that rats or mice housed with a running wheel (a model of aerobic exercise) can exhibit attenuated drug self-administration or drug-induced psychomotor hyperactivity in comparison with their sedentary counterparts (Bardo and Compton, 2015; Geuzaine and Tirelli, 2014).

However, the few experiments using conditioned place preference (CPP) are conflicting (positive, negative or null effects of exercise). Aspects of the methods used in some studies, in particular the low sample size, the absence of a baseline pre-conditioning session or a control group in the design or (when present) in the data analyses, make the whole picture of results difficult to understand, a situation which warrants further studies, possibly of a better quality.

Our purpose was to test whether wheel-running exercise during adolescence could impact the formation and long-term retention of CPP to cocaine in mice.

Methods



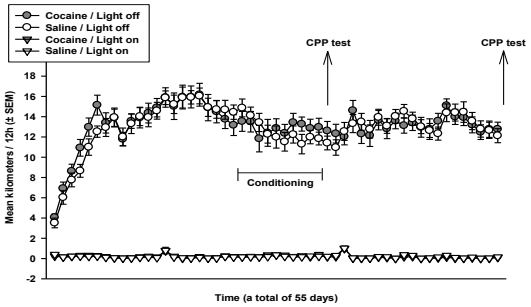
Experimental design. Male C57BL/6J mice were individually housed either with (n=32) or without (n=32) a running wheel from 35 days of age, each group receiving cocaine or saline during testing (n=16). The assignment procedure was based on a computer-generated randomization schedules. The choice of the sample size (n=16) was informal and based on the median number of animals used in previous CPP experiments (n=8) that we elected to double.
Behavioral testing begun 3 weeks after such housing, all animals being first tested under saline for their baseline preference (white or black compartments). Then, mice underwent 10 once-daily conditioning sessions receiving peritoneal injections of 10 mg/kg cocaine (C) and saline (S) on alternate days. The white compartment (always non-preferred) was systematically associated with cocaine effects (non-counterbalanced assignment procedure). Control mice received saline every day. One and 21 days after the last conditioning session, mice were tested for place preference under saline (T).

CPP apparatus

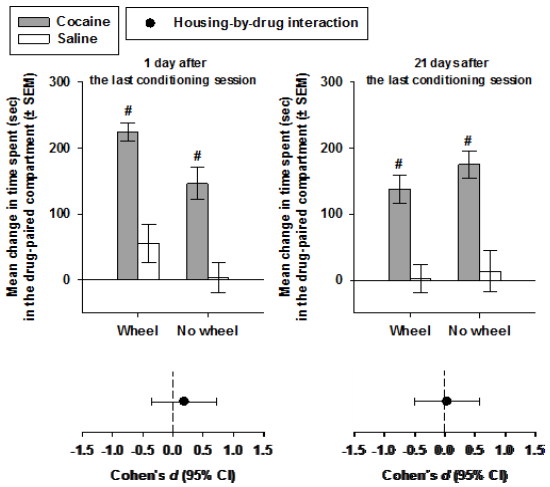
Running wheel

The CPP score consisted of the absolute difference between the pre- and post-conditioning sessions (by subtracting the amount of time spent in the drug-paired side before conditioning from the amount of time spent in the drug-paired side after conditioning). CPP scores were analyzed with *a priori* single (cocaine vs saline) and crossed contrasts (testing the housing-by-drug interaction). Each contrast (*t*-test) incorporated the mean-square error (MSE) provided by a preliminary two-way fixed-model 2x2 ANOVA incorporating the housing condition (2 levels) and the drug treatment (2 levels) as between-group factors and time of testing as a blocking factor (8 levels). Estimates of effect sizes were provided by Cohen's *d* calculated from *t*s and degree of freedom.

Results



Running activity. Nocturnal (light off) and diurnal (light on) wheel-running exercise (distance traveled in kilometers) in mice housed with a wheel (n=32) and receiving either cocaine (n=16) or saline (n=16) during conditioning.



Conditioned place preference. CPP scores to cocaine 1 day or 21 days after the last conditioning session (with n=16). #: significantly greater than the corresponding saline group.

The two groups exhibited significant well-marked cocaine-induced CPP in both 1-day (d = 1.38, $t(53)$ = 5.04 and d = 1.11, $t(53)$ = 4.04 at ps < .001 one-tailed in exercised and sedentary mice) and 21-day post-conditioning tests (d = 1.09, $t(53)$ = 3.95 and d = 1.15, $t(53)$ = 4.19 at ps < .001 one-tailed in exercised and sedentary mice).

The (small) effects underlying interaction between housing and the drug treatment were not significant for 1-day (d = 0.19, $t(53)$ = 0.71 at p = .48 two-tailed; 95% CI -0.35 to 0.73) or 21-day post-conditioning tests (d = 0.05, $t(53)$ = 0.17 at p = .87 two-tailed; 95% CI -0.49 to 0.59).

Discussion

Our results reproduce those previously obtained in our laboratory (Geuzaine and Tirelli, 2014) by showing that wheel-running exercise is ineffective at significantly altering CPP to 10 mg/kg cocaine in male C57BL/6J mice in comparison to a control housing. However, the results from the two other studies that have investigated the effects of wheel-running on CPP induced by cocaine differ with ours by reporting accentuated CPP after such exercise (Smith et al., 2008; Mustroph et al., 2011). This exercise-induced increase in CPP - somewhat contrasting with the protective effects of aerobic exercise on vulnerability to rewarding properties of drugs of abuse - has been hypothetically ascribed to an enhancement of associative learning capabilities resulting from neuroplastic changes induced by chronic wheel-running.

In that framework, one can speculate that the hypothetical inhibition of wheel-running of the rewarding component of CPP in our mice was concurrently reversed by the improving effect of such exercise on contextual learning (that underlies CPP), finally leading to neutralized effects. One can further suppose that attenuated or augmented CPP scores in animals housed with a running wheel would depend of the relative strength of both pro-cognitive and attenuating effects of the rewarding properties of drugs; this interaction may be modulated by experimental parameters.

If physical exercise in rodents "truly" impacts CPP induced by drugs of abuse under comparable experimental parameters - as suggested by some studies (either positively or negatively) - our results indicate that the size of such effects may be quite small, an information rarely reported in the literature.

References

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