Neurobiological evidence for hedonic allostasis associated with escalating cocaine use

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A paradoxical aspect of the transition to drug addiction is that drug users spend progressively more time and effort to obtain drug hedonic effects that continually decrease with repeated experience[1,2]. According to the hedonic allostasis hypothesis[3], increased craving for and tolerance to the hedonic effects of drugs result from the same chronic alteration in the regulation of brain reward function (allostasis). Here we show in rats that repeated withdrawals from prolonged cocaine self-administration produces a persistent decrease in brain reward function that is highly correlated with escalation of cocaine intake and that reduces the hedonic impact of cocaine.

During acute withdrawal from prolonged exposure to various drugs of abuse, intracranial self-stimulation (ICSS) thresholds—an operational measure of brain reward function—increase above basal levels but return to baseline hours afterwards[4–7]. This elevation in thresholds associated with acute withdrawal reflects a transient decrease in brain reward sensitivity that counterbalances the threshold-lowering effects of drugs[8,9]. Unknown, however, is whether this transient decrease in reward worsens and becomes chronic with repeated withdrawals and whether it is associated with the development of compulsive drug use. Male Wistar rats (300–350 g) with bipolar electrodes in the posterior lateral hypothalamus were trained in a discrete-trial, current-intensity ICSS protocol[10]. After stabilization of ICSS thresholds, rats were given differential access to a continuous schedule of intravenous cocaine self-administration (0.25 mg/injection): 0 hour (naive rats, $n = 6$), 1 hour (short-access or ShA rats, $n = 9$) or 6 hours per day (long-access or LgA rats, $n = 11$)[11]. Repeated prolonged access to cocaine or heroin (6 hours or more) produces an escalation in drug intake not observed with limited access (1 hour) to the drug[11,12]. ICSS thresholds were measured daily 3 hours and 17–22 hours after each self-administration session, the second time point occurring 1 hour before each next session. This design allowed us to probe the functional state of brain reward systems during the withdrawal periods separating repeated self-administration sessions (**Supplementary Methods** online). All experimental procedures were approved by the Animal Care and Use Committee of The Scripps Research Institute.

ICSS thresholds remained unchanged and stable for the duration of the experiment in both drug-naive controls and ShA rats (**Fig. 1a**). In contrast, ICSS thresholds in LgA rats were progressively elevated between sessions to 30% above baseline (**Fig. 1a**). ICSS thresholds deviated more and more from baseline in LgA rats because elevated ICSS thresholds failed to return to baseline before each next self-administration session. This effect was not due to a decreased ability to respond, as no difference between groups was observed in response latencies for ICSS (**Fig. 1c**). The gradual elevation in thresholds was associated with a dramatic escalation of both first-hour (**Fig. 1b**) and total cocaine consumption (from 75.5 ± 13.9 to 125 ± 4.3 injections; data not shown). The slope of elevation in reward thresholds measured 1 hour before access to cocaine was highly correlated ($r = 0.78$, $P < 0.01$) with the slope of escalation in total cocaine intake (**Fig. 1d**). Also, in all LgA rats, daily levels of total cocaine intake were positively correlated with daily ICSS thresholds (percent change from baseline) measured 1 hour before (range, 0.27–0.91) or 3 hours after (0.23–0.82) daily access to cocaine. This positive correlation was significant in 8 of 11 LgA rats ($P < 0.05$; mean $r = 0.73$; range, 0.57–0.91). These findings may suggest an insidious process of escalation whereby decreased reward function contributes to increased cocaine intake, which in turn further decreases brain reward function.

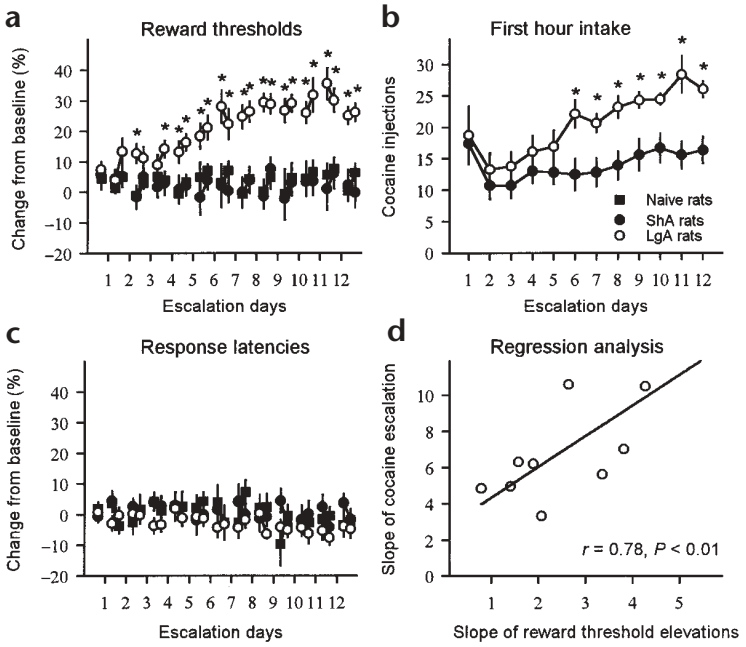

Fig. 1. Relationship between elevation in ICSS reward thresholds and cocaine intake escalation. (**a**) Percent change from baseline ICSS thresholds; (**b**) percent change from baseline response latencies (3 hours and 17–22 hours after each self-administration session; first data point 1 hour before the first session). (**c**) Number of cocaine injections earned during the first hour of each session. (**d**) Correlation between the slope of escalation in total cocaine intake and the slope of elevation in ICSS thresholds in LgA rats. Slope coefficients were computed by fitting the self-administration and ICSS data with a linear function. *$P < 0.05$ compared to drug-naive and/or ShA rats, tests of simple main effects.

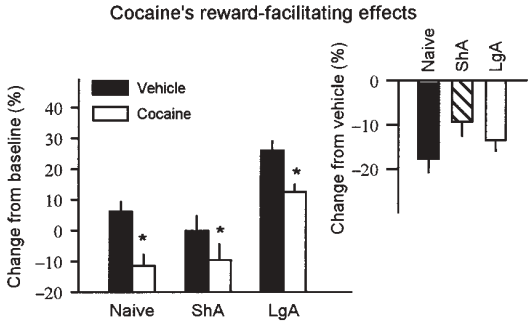

Fig. 2. Acute effect of cocaine on ICSS reward thresholds. Percent change from baseline ICSS thresholds following intravenous saline or cocaine administration (0.25 mg/injection). Bars in inset represent percent difference between thresholds after vehicle and cocaine administration. *$P < 0.05$ compared to vehicle, tests of simple main effects.

One day after escalation testing, all rats received an intravenous injection of vehicle and 3 hours later an injection of the unit dose of cocaine available during self-administration. ICSS testing began 1 min after each injection. In all groups, cocaine significantly lowered ICSS thresholds relative to thresholds measured after vehicle administration, reflecting the reward-facilitating effect of cocaine (**Fig. 2**). The net threshold-lowering effect of cocaine (thresholds after vehicle minus thresholds after cocaine administration) did not vary significantly between the groups (**Fig. 2**, inset). Nevertheless, in LgA rats, the chronic elevation in basal ICSS reward thresholds shifted the net threshold-lowering effect of cocaine upward, thereby preventing the threshold from reaching the same absolute level as in controls after the same challenge (**Fig. 2**).

Two days after escalation testing, daily access of LgA rats to cocaine was reduced from 6 hours to 1 hour for 8 consecutive days; this duration of access does not induce drug intake escalation (refs. 11,12 and present data). During the post-escalation phase, ICSS thresholds were measured only 1 hour before each self-administration session. Reward thresholds (**Fig. 3a**) and first-hour cocaine intake (**Fig. 3b**) of LgA rats remained significantly elevated above control levels for at least 8 days after cessation of prolonged access to cocaine.

This study supports the hedonic allostasis hypothesis of drug addiction[3] by showing that the transient counteradaptive reaction after acute withdrawal from prolonged cocaine exposure[5] shows a residual hysteresis with repeated withdrawals that is highly correlated with cocaine intake escalation and that leads to the establishment of a persistent deficit (at least eight days) in regulation of brain reward function. These findings suggest that hedonic responsiveness to the environment decreases progressively during repeated withdrawals from prolonged access to cocaine, increasing the animal's motivation to seek the threshold-lowering effects of cocaine to reverse this hedonic deficit. The persistence of this hedonic deficit may be part of the neurobiological basis for continued craving and increased vulnerability to relapse associated with drug addiction[3]. The present findings also suggest that tolerance to the hedonic effects of cocaine does not result from a decreased effect of cocaine on basal reward thresholds, consistent with findings of no change in cocaine pharmokinetics or pharmacodynamics after cocaine intake escalation (S.H.A. *et al.*, unpublished data). Rather, tolerance results from the establishment of a new basal reward threshold that shifts the unchanged threshold-lowering effect of cocaine upward and therefore prevents thresholds from reaching the same absolute level as before repeated, prolonged exposure to cocaine. Thus, more doses are progressively needed to maintain the same hedonic effect, further aggravating the dysregulation of brain reward function. Thus, hedonic allostasis provides a parsimonious explanation to one of the enduring paradoxes of drug addiction by showing how a subject becomes both hedonically dependent on a drug and tolerant to its hedonic effects. Treatments that block elevation in brain reward thresholds produced by chronic cocaine thus would be predicted to block escalation of cocaine intake and could be tested as new therapies for addiction[13].

Note: Supplementary information is available on the Nature Neuroscience website.

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Competing interests statement

The authors declare that they have no competing financial interests.

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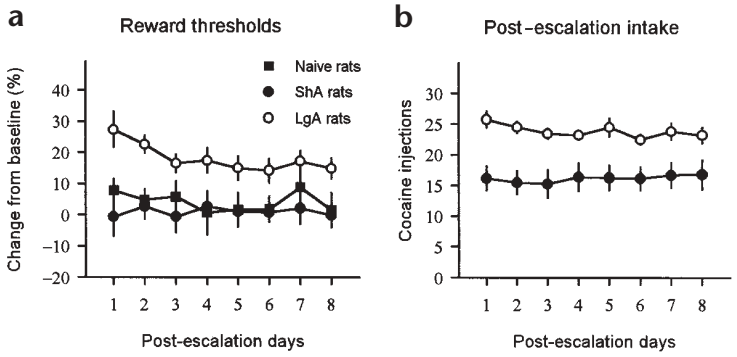

Fig. 3. Persistent elevation in ICSS reward thresholds after cessation of prolonged access to cocaine self-administration. (**a**) Percent change from baseline ICSS thresholds. ICSS measurements were made daily one hour before access to cocaine. (**b**) Number of cocaine injections earned per one-hour session. In both graphs, LgA rats were significantly different from other groups throughout post-escalation testing ($P < 0.05$, Newman-Keuls tests).

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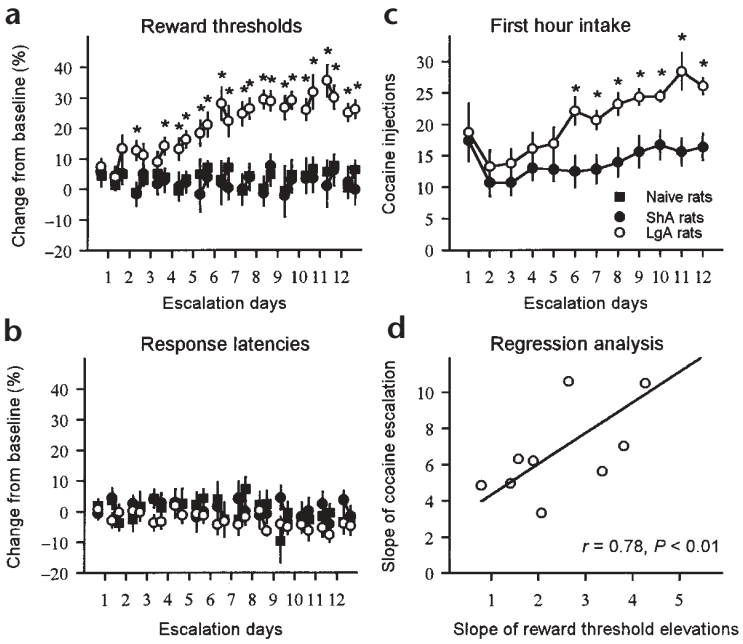
A mistake was introduced during the preparation of this paper. In the AOP version, panel labels b and c in Fig. 1 were mistakenly switched. The lower left panel should be labeled b, and the upper right panel should be labeled c. This mistake has been corrected in the HTML version and will appear correctly in print. The PDF version available online has been appended.



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