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REVIEW

Cocaine modulation of the mammalian circadian clock: potential therapeutic targets

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The circadian system plays an integral role in regulating physiological and behavioral responses to cocaine, which contribute to abuse and relapse. To date, however, little is known of the mechanism(s) underlying cocaine effects on biological timing, and in particular, how this drug may impact the regulation of the master circadian clock of the suprachiasmatic nucleus (SCN). This review summarizes our current research into the chronotypic actions of acute and chronic cocaine. In initial experiments, it was shown that acute systemic and *in vitro* cocaine blocks the nocturnal SCN photic phase-resetting response critical for circadian entrainment to the light-dark cycle (LD). Cocaine treatment at midday also advances circadian clock phase, showing that this drug possess non-photic circadian phase-resetting properties. Next, chronic (weeks-months) cocaine regimens were used to model human drug abuse patterns. Such long-term oral drug exposures caused dramatic alterations in intrinsic circadian period and entrainment to LD that persisted long after cocaine withdrawal, suggesting long-term (possibly permanent) circadian disruptive effects. Lastly, we found that the acute systemic cocaine effects described above are blocked using a serotonin receptor antagonist (metergoline) targeted to the SCN *in vivo*, as well as *in vitro*, suggesting involvement of a serotonergic mechanism. Consistent with this hypothesis, mutant mice with a cocaine-insensitive serotonin transporter exhibited little or no circadian response to cocaine. Collectively, these results indicate that cocaine-induced perturbations of clock timing could produce chronic psychological and physiological stress, contributing to increased cocaine use and dependence. Earmarking the serotonergic system in mediating these cocaine effects offers a potential chrono-pharmacological approach for the treatment of cocaine abuse and addiction.

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The importance of circadian rhythms for both physiological and behavioral processes associated with cocaine abuse has only recently begun to be understood. Cocaine self-administration in rats and mice was shown to be restricted to the dark portion of the light-dark cycle, providing evidence for circadian regulation of drug seeking behavior [1, 2, 3]. The psychomotor response to cocaine, as well as its reinforcing effects, also exhibit strong circadian rhythmicity [4, 5]. At the molecular level, recent studies have demonstrated that circadian clock genes, including *BMAL1*, *CLOCK*, *PER*, and *CRY* that facilitate circadian clock timing are critical in regulating the physiological and reinforcing effects of cocaine. For example, mutant *Drosophila melanogaster* that lack these core genes do not develop an increased physiological response to repeated cocaine administration (sensitization) [6]. Additionally, *PER1* knockout mice display a decreased behavioral sensitization to cocaine as well as decreased acquisition of conditioned place preference (CPP), in contrast to *PER2* and *CLOCK* mutant knockout mice, which show exaggerated sensitization

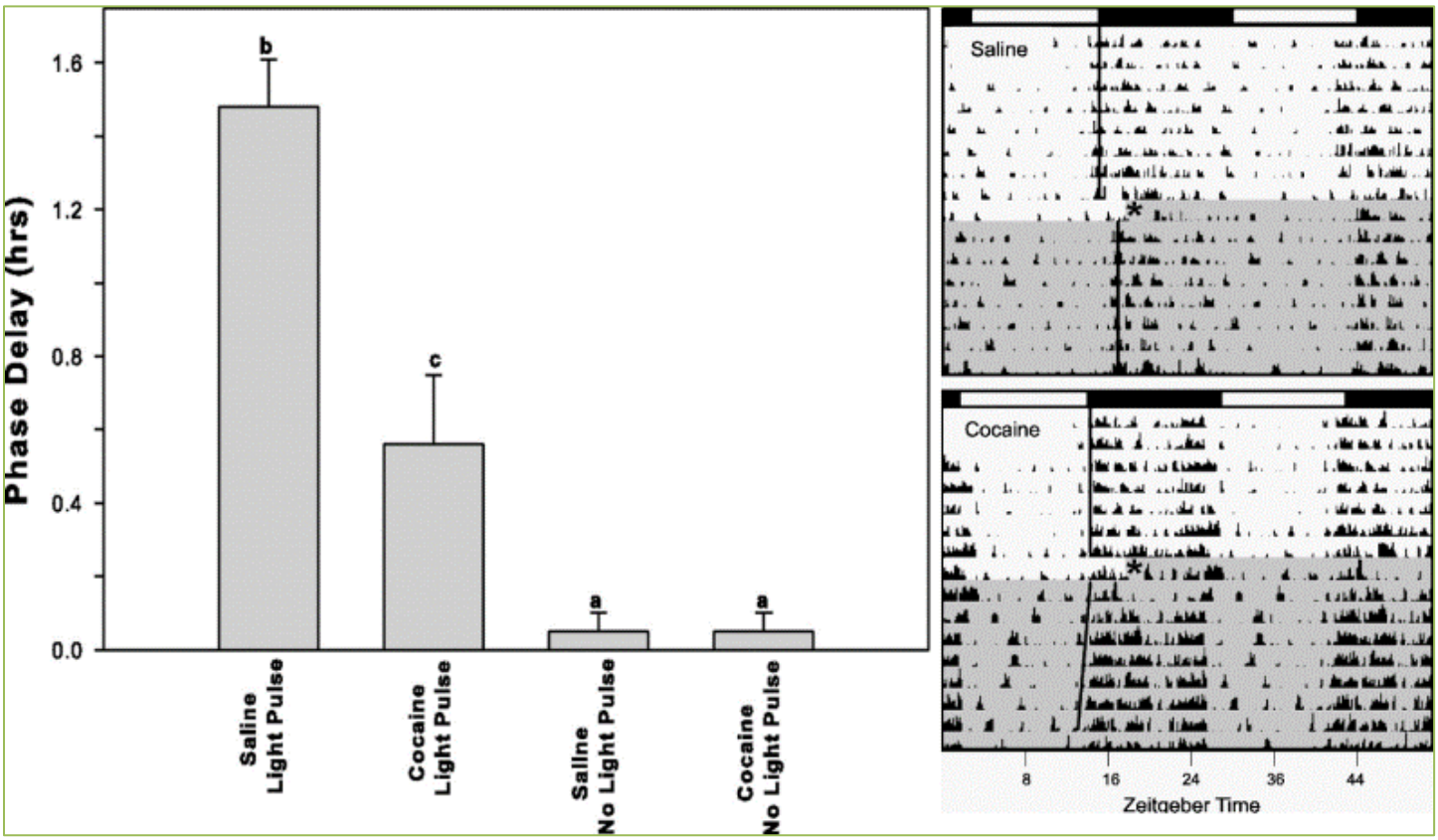

Figure 1. ***Left:*** **Histogram showing that photic phase resetting during the early dark phase (ZT 16) is disrupted by acute cocaine pretreatment.** [a,b,c]Bars with different letters show significant difference ($P < 0.05$). Expressed values are means ± S.E.M.; n = 7/group. ***Right:*** Representative double-plotted actograms of general locomotor activity illustrating attenuated photic phase-resetting to a light pulse by cocaine pretreatment at ZT 16 (asterisk designates time of injection and light pulse). Horizontal filled bars represent the dark phase of the 24-h light-dark cycle; shaded areas, constant darkness. Reprinted with permission[20].

and CPP, indicating a complex and antagonistic regulatory role for clock genes in substance abuse [4, 6]. There is also evidence that cocaine up-regulates the expression of clock genes in brain reward areas [8, 9]. At the systemic level, cocaine disrupts circadian-regulated homeostatic functions, including endocrine, autonomic, and immune processes, as well as sleep and feeding [10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. Despite this information, the physiological bases of cocaine's actions within the circadian system remain to be characterized. In this review we will summarize recent studies focusing on mechanisms underlying cocaine's disruption of the circadian timing system, including the neurochemical basis for this action in the male C57BL/6 mouse.

Acute Cocaine Effects

An initial series of experiments was undertaken to determine whether a single acute application of cocaine could affect critical photic and non-photic regulatory pathways of the mouse circadian timing system. We first explored its effects on the photic signaling pathway in the SCN. The SCN maintains entrainment with the environment by making daily advancing or delaying adjustments based upon light information mediated by glutamate release from retinal afferents. When exposed to light during the early dark phase, the SCN normally delays circadian phase to synchronize with the external 24 h LD cycle. However, when challenged with an acute i.p. injection of cocaine administered prior to a phase-delaying light pulse, the photic phase-resetting response of the mouse SCN pacemaker is blocked (**Fig. 1**) [20]. Notably, this effect is centered in the SCN, since cocaine blocks the photic-like phase advance and phase delay responses to glutamate applied to the SCN isolated in a brain slice preparation [20]. In addition to its photic effects, cocaine also acts as a non-photic phase-resetting agent, since acute i.p. injection of cocaine at midday advances clock phase. Again, this action appears to involve actions occurring in the SCN, as direct perfusion of cocaine into the SCN via reverse *in vivo* microdialysis, and administration of cocaine *in vitro* to SCN brain slices both elicit significant phase-advances [20].

Interestingly, there is evidence that the photic and non-photic responses to cocaine described above are

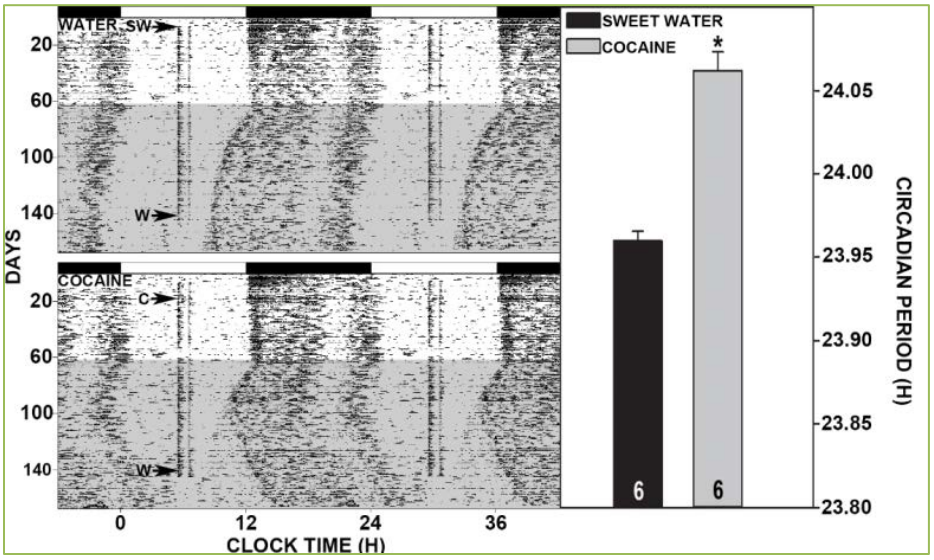

Figure 2. ***Left:*** **Representative double-plotted actograms of general locomotor activity for mice receiving a daily 1-h pulse of sweetened water (top actogram) or sweetened cocaine solution (0.5 mg/ml; bottom actogram) at midday.** The shaded area represents constant darkness. C, cocaine onset; SW, sweetened water onset; W, withdrawal. Horizontal filled bars represent the dark phase of the 24-h light-dark cycle. Note the difference in free-running period between the control and drug treated mice before and 3 weeks following withdrawal. Exposure to either fluid evoked behavioral arousal evident in the actograms. *Right*: Histogram depicting the mean ± S.E.M. free-running period between control and cocaine mice. Group *n*'s are shown as numbers appearing within the bar for each group. Asterisk indicates significant differences between means. Reprinted with permission [3].

regulated by the *Per2* clock gene. In response to light pulses, *Per2* mutants with non-functional Per2 protein exhibited larger photic phase-delays than WTs, and the attenuating action of cocaine on this response was proportionately larger than in WTs [21]. Likewise, when cocaine is administered systemically by acute i.p. injection at midday, the non-photic phase-advancing response to the i.p. cocaine at midday was significantly (~3.5-fold) greater in *Per2* mutants than wild-type (WT) mice. In contrast, phase-advances induced by daytime *intra-SCN* cocaine perfusion did not differ between genotypes. Together, these data indicate that the *Per2* clock gene is a potent modulator of cocaine's actions in the circadian system. With regard to non-photic phase-resetting, the SCN is confirmed as a direct target of cocaine action; however, *Per2* modulation of this effect likely occurs outside of the SCN.

Chronic Cocaine Effects

As discussed above, the circadian-related disruptive effects of cocaine on physiological, behavioral and genetic processes are well established. However, few studies have focused on the actions of cocaine on adult central circadian clock timekeeping *per se*, and none have explored the circadian implications of chronic (weeks to months) exposure. This latter approach has technical limitations, however, since the physical interference associated with operant catheter systems and systemic injection of cocaine administration can hamper measurements of circadian behavior. We therefore employed the minimally invasive method of supplying cocaine in drinking water. Orally administered cocaine produces plasma drug concentrations comparable to other modes of administration, albeit with longer duration [22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. This method has allowed us to evaluate the effects of various regimens of chronic cocaine exposure on basic circadian behavioral functions, including entrainment to the light–dark (LD) cycle, daily activity patterns and intrinsic circadian clock period.

In these experiments, mice housed under LD conditions and provided with daily timed access to cocaine for two months did not differ behaviorally from control (water only) mice in basic circadian traits including phase-angle of entrainment (phase relationship between the endogenous period of the master pacemaker and the external photic environment), time of activity onset and offset, or length of daily activity (alpha) [3]. In contrast, mice placed under constant darkness (DD) and provided with daily timed access to cocaine for 2 months displayed a significantly longer endogenous free-running rhythm period than water controls (**Fig. 2**). Importantly, when access to cocaine was removed the free-running period of the cocaine exposed mice remained lengthened for over a month and may have been

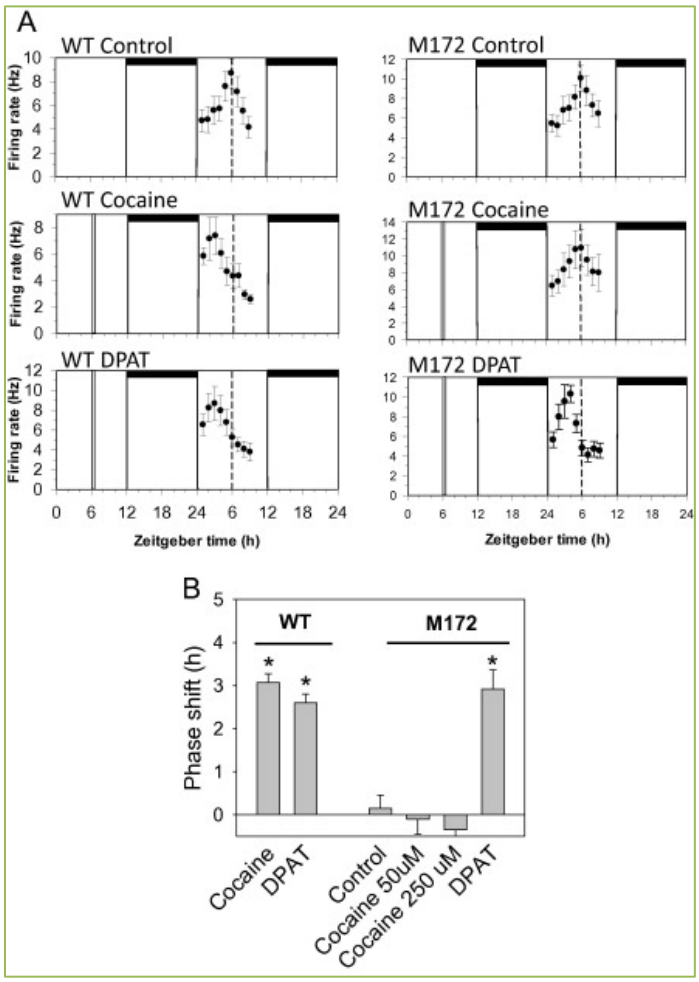

Figure 3. *In vitro* non-photic phase resetting of the SCN circadian clock. A: Representative neuronal SCN activity profiles shown as 2-h mean ± S.E.M. Peak *in vitro* neuronal activity occurred near ZT 6 (no drug) and was advanced by cocaine treatment (ZT 3; 50 μM). In contrast, cocaine application to SCN brain slices from SERT Met172 mice induces no phase shift, while DPAT treatment advances peak neuronal activity both in WT and SERT Met172 mice. Horizontal bars: time of lights-off in the animal colony; vertical bars: time of drug treatment; dotted line: mean time-of-peak in untreated brain slices. B: Histogram plot of mean ± SEM phase shifts induced by the different *in vitro* treatments at ZT 6. $^{*}p < 0.01$ vs. mean time-of-peak in untreated WT brain slices. Reprinted with permission [47].

permanently altered. Subsequently, we determined that cocaine exposure for three weeks is sufficient to induce the long term lengthening of circadian period [3].

Likely related to the altered free-running period, chronic cocaine exposure can affect entrainment to a modified LD cycle. Mice were subjected to a 5 hour delay-shift in the onset of darkness and subsequently placed under a skeleton-photoperiod of a single minute of low intensity light per day (to minimize photic masking [behavioral, rather than circadian response to light]). When exposed to cocaine, these mice re-entrained to the new photoperiod more rapidly than water controls [3]. Notably, these cocaine treated mice used the short light pulse to initiate daily activity, as opposed to the water controls whose daily activity ended at the light pulse, resulting in the two groups being 147° out of phase with one another. Consistent with the chronic cocaine effects seen above, this disrupted entrainment persisted after cocaine access was withdrawn until the end of the study (2 months), indicative of the persisting nature of cocaine action in the circadian system.

It is important to note that while free-running rhythm and entrainment to light were both significantly altered by prolonged cocaine exposure, behavioral entrainment to the normal LD cycle is largely unaffected, likely due to the behavioral masking action of light. Thus, it will be important to determine what action cocaine has on the coherence of internal physiological rhythms (i.e. daily body temperature or hormonal release patterns). Perturbation of such rhythms could lead to the documented deleterious health effects of prolonged cocaine use discussed above. Theoretically, such drug-induced alterations in circadian rhythmicity could underlie increased incidence of cardiovascular disease [34], obesity [35, 36], cancer [37, 38] and sub-optimal fecundity [39].

Mechanism of Cocaine's Action in the Circadian System: The Serotonin Hypothesis.

Within the central nervous system, cocaine binds reuptake transporters for dopamine, serotonin, and norepinephrine thus increasing the bioavailability of these neurotransmitters within the synapse. While there is significant evidence that the reinforcement by cocaine is effected mainly through dopaminergic reward pathways [7, 40, 41, 42, 43, 44, 45], pretreatment of SCN brain slices with the dopamine antagonist fluphenazine does not have any effect on subsequent cocaine mediated phase shifts [20]. However, pretreatment with the serotonin antagonist metergoline abolishes cocaine disruption of photic-phase resetting during the dark phase as well as cocaine induced phase-advances during midday (see above) *in vivo* and *in vitro*, suggesting a serotonergic mechanism for cocaine's action within the circadian system [20]. The idea that cocaine may modulate the SCN circadian clock through enhanced serotonin signaling is further supported by data showing that the *in vitro* phase shifts induced by cocaine are mimicked by *in vitro* applications of serotonin [46] and serotonin agonists such as 8-OH-DPAT (**Fig 3**) [47]. This hypothesis was further tested using a transgenic mouse line (SERT Met172) which contains a single amino-acid substitution (IIe172Met) resulting in normal 5-HT transmission and reuptake, but a 50-fold decrease in 5-HT reuptake blockade in response to cocaine compared to WT mice [48, 49]. In contrast with the effects of acute and chronic cocaine discussed above, SERT Met172 mice do not exhibit cocaine-mediated disruption in

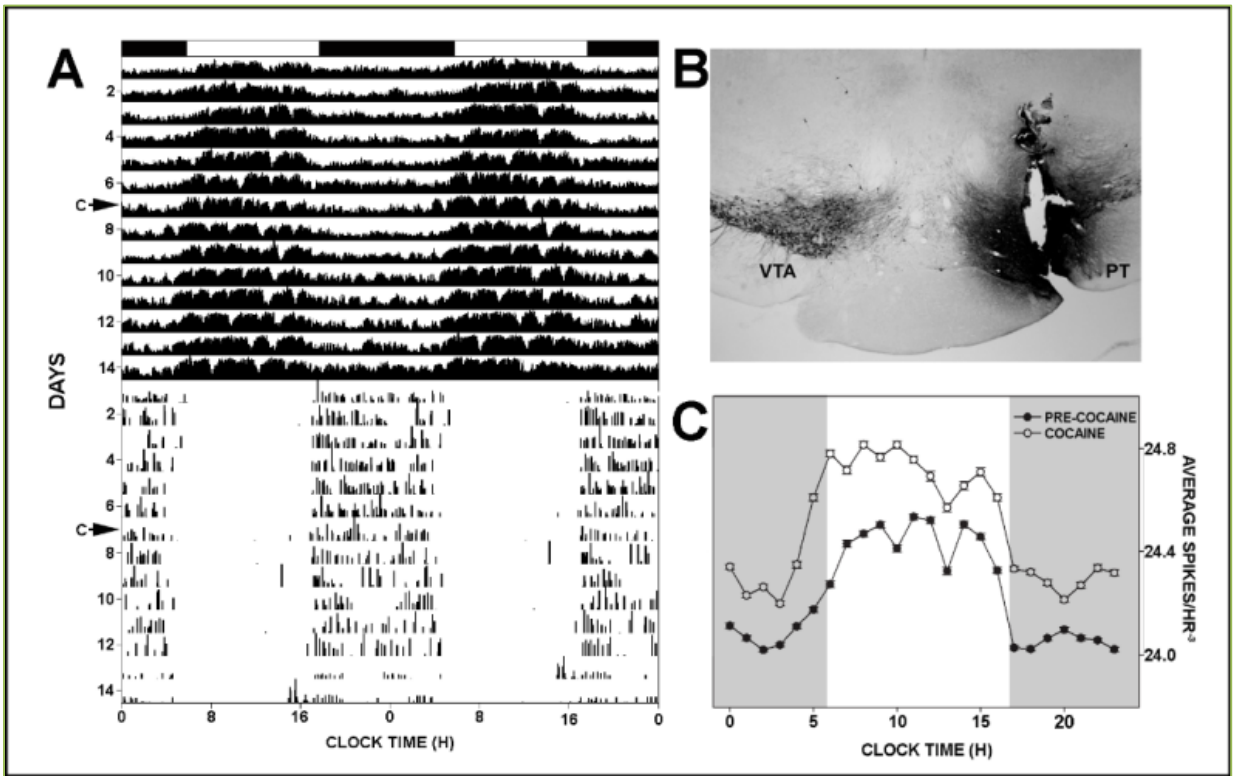

Figure 4. A: Representative double-plotted actograms showing the circadian nature of spontaneous electrical output (MUA) from the VTA (top) and daily episodic drinking behavior (bottom). Note that the VTA rhythm is anti-phase to the behavioral rhythm. Horizontal filled bars represent the dark phase of the 24-h light-dark cycle. "C" indicates initiation of forced cocaine regimen. B: Photomicrograph of coronal brain section stained for tyrosine hydroxylase showing location of the recording electrode tip (PT) placed in the VTA (left portion of section). Following the end of the experiment, current was passed through the electrode to visualize electrode tip placement, resulting in the lesion evident in the right portion of section. C: Line plot illustrating mean hourly spikes/minute values during the light and dark phases (grey shading) of the light-dark cycle before and during cocaine self-administration. [a,b,c,d] Bars with different letters show significant difference ($P< 0.05$). Values are expressed as means ± S.E.M.

photic-phase resetting to a light pulse during the late portion of the dark phase, or any phase-advance in response to acute cocaine administration during midday, *in vitro* and *in vivo* (**Fig. 3**) [47]. Additionally, SERT Met172 mice given forced, continuous access to cocaine dissolved in drinking water for three weeks do not exhibit the lengthening of free-running period which was previously seen in WT controls [47]. Taken together, these studies provide strong evidence for a critical role of serotonin signaling in mediating cocaine effects in the adult mammalian circadian system.

Future Directions

While there is evidence that acute and chronic cocaine treatment regimens can cause marked disruption of circadian photic and non-photic pathways, little is known of the neural mechanism(s) underlying these effects. Our findings strongly suggest that serotonergic pathways in the SCN are a direct substrate for cocaine's chronotypic effects. However, microinjection of cocaine directly into the ventral tegmental area (VTA) at midday also phase-advances the locomotor rhythm [50]. Thus, cocaine may also alter circadian phase via a secondary action in the mesolimbic reward pathway. We have begun assessing these non-SCN effects of cocaine by examining the action of cocaine on the circadian pattern of multiunit activity (MUA) of VTA neurons. These measurements show that oral cocaine intake significantly increases the amplitude and alters the phase of the circadian rhythm of VTA MUA (**Fig. 4**) [51]. Another potential avenue of research relates to the effects of cocaine on circadian period that persist long after drug withdrawal. Such long lasting (and possibly permanent) effects of cocaine could involve epigenetic alteration of clock gene or other circadian regulatory elements. Epigenetic and trans-generational actions of cocaine on non-circadian behavioral endpoints have been recently documented [52, 53], and suggest even more pervasive effects of this drug than previously thought.

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