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The Intertwined Roles of Circadian Rhythms and Neuronal Metabolism Fueling Drug Reward and Addiction

Zachary Freyberg[1,2] and **Ryan W. Logan**[1,3,*]

[1]Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh, pittsburgh, PA, USA 15219

[2]Department of Cell Biology, University of Pittsburgh, Pittsburgh, PA USA 15213

[3]Center for Systems Neurogenetics of Addiction, The Jackson Laboratory, Bar Harbor, ME, 04609

Abstract

Drug addiction is a highly prevalent and devastating disorder with few effective treatments, resulting in enormous burdens on family and society. The cellular and behavioral effects of drugs of abuse are related to their abilities to elevate synaptic dopamine levels. Midbrain dopaminergic neurons projecting from the ventral tegmental area to the nucleus accumbens play crucial roles in substance-induced neural and behavioral plasticity. Significantly, increasing work suggests that interplay between the brain circadian system and the cellular bioenergetic machinery in these dopamine neurons plays a critical role in mediating the actions of drugs of abuse. Here, we describe recent progress in elucidating the interconnections between circadian and metabolic systems at the molecular and cellular levels and their relationships to modulation of drug reward and addiction.

Keywords

Circadian; drug abuse; reward; metabolism; NAD^+

Introduction

Abuse and dependence of substances comprise some of the most globally prevalent disorders today [1]. However, our understanding of the fundamental mechanisms underlying drug abuse and dependence remain limited. The consensus is that behavioral effects of drugs of abuse are mediated predominantly by their actions in the central nervous system (CNS) through modulation of neurotransmission. Much evidence suggests that drugs' cellular and behavioral effects are related to their ability to elevate synaptic dopamine (DA) levels [2].

*Corresponding Author: Ryan W. Logan, PhD, Assistant Professor, Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh School of Medicine, 450 Technology Drive, Office 224, Bridgeside Point II, Pittsburgh, PA USA 15219, Tel: 412.383.3084, FAX: 412.624.5280, rwl16@pitt.edu.

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Midbrain DA neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) play critical roles in drug-induced neural and behavioral plasticity [3]. Most, if not all, of these drugs change patterns of VTA-NAc neurotransmission and plasticity at molecular, cellular, circuit levels [3–6]. Emerging data also suggests cellular and molecular rhythms are important regulators of drug reward, and circadian genes [7–11] have been directly implicated as modulators of the DA reward circuitry [12–16]. Additionally, disturbances in circadian regulation of the DA system alter the rewarding properties of drugs of abuse, further increasing vulnerability to substance abuse and addiction [12,17–22]. Ultimately, these drug-induced effects on the CNS circadian system are energy-demanding [12,23,24]. Yet, we know little about how neurons and other neural cell-types meet these bioenergetic demands in response to drugs of abuse. This leads to the following questions: 1) How do changes in neuronal rhythmicity and metabolism contribute to drug reward and dependence? and,2) If so, are circadian clocks directly involved in mediating these effects? Here, we focus on describing the interconnections between neuronal circadian rhythms and cellular bioenergetics, as well as their relationships to modulation of drug reward and addiction.

The CNS circadian system

In mammals, many physiological functions and behaviors are regulated by circadian rhythms. Such rhythms are coordinated by the master circadian pacemaker, the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, which relays light as ‘timing’ information from the eyes to the rest of the brain and body [25]. Virtually all cells express the machinery for generating molecular rhythms, comprised of a series of transcriptional and translational feedback loops cycling with near 24-hour periods. These rhythms are driven by the circadian transcription factors CLOCK and BMAL1 that form heterodimers (CLOCK:BMAL1) [26,27]. These heterodimers are recruited to enhancer promoter elements (E-boxes) to promote gene transcription, including the circadian genes *Period (Per1,2)* and *Cryptochrome (Cry1,2)* [28,29]. PER and CRY proteins accumulate in the cytoplasm and are transported to the nucleus to inhibit their own transcription via direct interactions with CLOCK:BMAL1 [30,31]. Additional proteins modulate the phasing and amplitude of molecular clocks. Recent transcriptomic surveys suggest a range of 40–80% of genes within the mammalian genome are regulated in a rhythmic manner, depending on the assay methodology and species [32,33]. Core circadian genes, including *Clock, Bmal1, Per2,* and *Cry2*, are the most consistently rhythmic genes between tissues, indicating other clock-controlled genes (CCGs) may be tissue and/or cell-type specific [27,33,34].

Within the CNS, differential enrichment of circadian transcription factors may be responsible for regulation of circadian-dependent functions [35,36]. For example, while CLOCK is largely expressed across many brain regions, expression of the paralog NPAS2, a circadian transcription factor structurally and functionally similar to CLOCK, is primarily limited to the mammalian forebrain and striatum [19,35,37,38]. Significantly, striatal expression of NPAS2 has been implicated as a modulator of drug reward and addiction [19,39]. Recent work also suggests NPAS2 may drive circadian transcription of genes with important roles in neuronal metabolism and energy homeostasis [40–45]. These findings suggest circadian and metabolic coupling, where molecular clocks may directly regulate the

expression and function of key metabolic cofactors and mitochondrial biogenesis in the brain. Furthermore, changes in cellular metabolism or redox state can feedback to modulate the function of circadian proteins [12,46–52]. Given the intimate connections between rhythms and metabolism in other highly metabolic tissues including liver and muscle [43,46,47,53,54], cellular and molecular clocks are plausible regulators of metabolism and energetics in the brain. However, the metabolic processes underlying neuronal firing and activity are poorly understood, particularly in relation to substance abuse. Recent findings demonstrating neuronal CLOCK-and NPAS2-dependent modulation of neuronal metabolism nevertheless pave the way for exploring the implications of these processes on drug reward and related behaviors.

Reciprocal Connections between CNS Molecular Clocks and Energetic Signaling

The brain consumes more oxygen and glucose than any other organ, relying mostly on the supply of energy substrates from the vasculature to fuel neurotransmission [55,56]. Adenosine triphosphate (ATP) is the primary carrier of energy and is secreted via calcium-dependent exocytosis from astrocytes [57]. Neuronal ATP is generated via several pathways including glycolysis and lactate production, as well as through mitochondrial oxidative phosphorylation and the tricarboxylic acid (TCA) cycle [58–60]. In brain as well as other metabolically-active tissues, ATP synthetic pathways are regulated by circadian-dependent environmental (*e.g.*, feeding rhythms) and biological rhythms (*e.g.*, molecular clocks) [61–64]. The molecular clock directly controls the transcription of metabolic cofactors including nicotinamide adenine dinucleotide (NAD^+), and rate-limiting enzymes of energy substrate production [50,52,65]. Furthermore, in SCN, mitochondrial calcium rhythms are necessary for circadian rhythms of extracellular ATP [66,67]. Diurnal variation of calcium homeostasis, extracellular glutamate, and ATP release also feedback to molecular clocks to modulate gene expression rhythms [68]. Whether ATP release follows diurnal rhythms in other brain regions remains to be investigated [64]. Nevertheless, since ATP can be co-released with or facilitate the release many neurotransmitters including glutamate, GABA and DA [69–73], and this neurotransmission is regulated in a circadian manner [21,74–77], we speculate that ATP release may also be diurnally controlled in areas beyond the SCN.

Extracellular ATP modulates synaptic function and plasticity via binding and activation of several subtypes of purine receptors on pre-and postsynaptic neurons and nearby astrocytes. For example, ATP activation of presynaptic ionotropic P2X receptors (P2XR) enhances glutamatergic neurotransmission [78–80], whereas binding to the metabotropic P2YRs inhibits further release [81–83]. Several subtypes of these receptors have been linked to reward and motivation. In mice, global deletion of the P2X4R in mice leads to increased alcohol intake during both intermittent and continuous access paradigms [84]. The expression of the receptor in various brain regions, including the VTA, also negatively correlates with alcohol preference in selectively bred mice and rats [85]. In general, reduced expression of P2X4R is associated with high alcohol preference, although increased expression has been found in certain high alcohol preferring rats [86–88]. In the VTA, P2X4Rs are densely expressed at GABAergic synapses, suggesting these receptors modulate

inhibitory neurotransmission [84]. These receptors also modulate dopaminergic and glutamatergic neurotransmission in mesolimbic neural circuitry [89,90]. ATP activation of P2X4Rs increased firing and release from midbrain DA neurons, leading to elevated extracellular DA in the NAc [89,91]. Presynaptic markers of DA synthesis and uptake, along with CREB-dependent pathways, may also be directly regulated by P2X4Rs [92]. At GABAergic and DAergic synapses, alcohol may inhibit the binding affinity of ATP to purine receptors, including P2X4R [93], ultimately altering neurotransmission. Other purine receptor subtypes such as P2Y1 may additionally be involved in drug reward, since blocking P2Y1Rs prevents amphetamine locomotor sensitization [94]. Given the links between ATP, purinergic receptors, and circadian pathways [95–97], these findings suggest complex, potentially reciprocal and bidirectional connections, implicating certain purine receptor subtypes as potential mediators of the impact of drugs of abuse on cellular rhythms and energetics. Purinergic signaling is also implicated in several other psychiatric disorders [98,99], where dysfunction of mitochondrial dynamics, energy homeostasis, and possibly circadian rhythms may be hallmarks of the disease.

ATP is used to synthesize another purine, the neuromodulator adenosine [99], which is also involved in drug reward and addiction. In the brain, extracellular adenosine displays robust, circadian dependent rhythms, where levels peak during the night and gradually building during the day. Adenosine is intimately involved in sleep and wakefulness, arousal, and circadian rhythms [100–105]. Adenosine activates P1 receptors (A1, A2A, A2B, and A3), which are primarily located on presynaptic terminals. Several of these receptors have been implicated in addiction [106], such as the A2AR, which is highly expressed in the striatum [107]. During withdrawal from cocaine, A2ARs are upregulated in both hippocampus and striatum of the rat [108–111], although these receptors seem to differentially modulate the behavioral effects of repeated cocaine administration. Indeed, deletion of A2ARs in striatal neurons enhanced cocaine sensitization, while deletion of the receptors in cortical and hippocampal neurons attenuated locomotor sensitization [112,113]. These receptors are involved in many other drug reward related behaviors [106].

Several mechanisms have been proposed for A2ARs to impact the behavioral response to drugs of abuse. A plausible mechanism involves the formation of heteromeric receptor complexes between A2ARs and D2Rs on GABAergic striatal neurons [114–116]. Consistent with this, activation of A2AR reduces D2R affinities for DA, enhances GABA release, and attenuates cocaine seeking behaviors [117,118], suggesting A2AR inhibits further activation of D2Rs on striatal neurons in response to cocaine. However, these receptor interactions may also be synergistic by further activating D2Rs, making such receptor associations especially relevant for drug withdrawal [119,120]. There may be therapeutic utility for targeting these receptors for the treatment of addiction, depending on the ability to further understand where and under which circumstances these specific receptor interactions are occurring [121]. Targeting these receptors may also alleviate the sleep and circadian rhythms disturbances which are common during drug withdrawal and abstinence. Furthermore, whether these circadian pathways are directly involved with these processes, including any interaction with D2R activity, remains an interesting avenue of future investigation, especially in relevant neural circuitry [122].

Circadian brain lactate production and drug-induced plasticity and relapse

Besides glucose, lactate is a major brain energy source. Astrocytes use extracellular glutamate to activate glycolysis, converting glycogen to pyruvate then lactate. Lactate is actively transported to neurons, entering the TCA cycle to produce ATP and for mitochondria to sustain oxidative phosphorylation. Together, these processes fuel neuronal metabolism to meet activity dependent demands [123]. Variations of extracellular lactate in cortical regions depend on the sleep-wake cycle, resembling biomarkers of energy homeostasis and sleep state [124,125]. Diurnal rhythms associated with neuronal activity and neurotransmission may therefore drive temporal changes in glycolysis and lactate in astrocytes.

Genes encoding proteins required for lactate production and transport are also direct transcriptional targets of circadian transcription factors. The monocarboxylate transporters of lactate between astrocytes and neurons, MCT1 and MCT2, are diurnally expressed in brain [41]. Moreover, NPAS2 drives transcription of lactate dehydrogenase A (LDHA), an enzyme that catalyzes lactate production [43]. Interestingly, expression of *Mct1*, *Mct2* and *Ldha* are markedly reduced in the NAc of NPAS2-deficient mice (unpublished results), consistent with impaired lactate production and transport to neurons (Fig. 1). Similar impairments of glycolysis either via direct blockade or by preventing lactate transport through MCT1 or MCT2 knockdown reduce the acquisition and maintenance of cocaine conditioned place preference and the number of infusions during cocaine self-administration [23,24]. Intriguingly, NPAS2 knockdown in the NAc also attenuates the acquisition of cocaine conditioned place preference, further suggesting the induction of NPAS2 is important for cocaine conditioned reward[19]. Given these data, we speculate that NPAS2 may be a transcriptional regulator of energy production in the NAc via the induction of *Ldha* and lactate production necessary for drug-paired contextual conditioning. Repeated administration of drugs of abuse disrupts molecular clocks in the striatum, which could have consequences on neuronal energetics and homeostasis, impacting drug reward and addiction.

Circadian regulation of mitochondrial redox and drug reward

NAD^+, a byproduct of lactate production, is an essential metabolic and redox cofactor crucial for the generation of ATP [126,127]. NAD^+ is also important in maintaining brain energy homeostasis, calcium transport, and mitochondrial respiration [127–129]. The recycling of NAD^+ requires several enzymes, including nicotinamide phosphoribosyltransferase (NAM T), the rate-limiting enzyme for the conversion of nicotinamide mononucleotide (NMN) to NAD^+. In liver and brain, the CLOCK:BMAL1 complex drives the rhythmic transcription of *Nampt* and thus, the circadian bioavailability of NAD^+ [12,52]. NAD^+ and NADH availability also modulate the DNA binding activity of CLOCK and NPAS2, indicating these transcription factors are integral redox sensors [41,43,130]. Low NAD^+:NADH ratios enhance DNA binding activity of NPAS2:BMAL1 and CLOCK:BMAL1 dimers, providing another level of energetic feedback to the molecular clock [43] (Fig. 1). Coupling between intracellular redox, metabolism, and circadian rhythms may be particularly important for maintaining temporal dependent changes in neuronal activity and governing the response to stimulation [131].

NAD^+ also interacts with mitochondrial SIRT1, a histone and protein deacetylase, to amplify molecular rhythms in the SCN [65]. Available NAD^+ enhances the deacetylase activity of SIRT1, which deacetylates BMAL1 to repress CLOCK:BMAL1-mediated transcription[49]. On the other hand, SIRT1 also deacetylates PER2 to promote its degradation and amplify CLOCK:BMAL1-mediated gene transcription [132] – actions that may directly impact the actions of drugs of abuse. Repeated cocaine or morphine administration increases expression of SIRT1 and circadian genes including *Per1* and *Per2* at specific diurnal phases [39,133–135]. Moreover, NAc-specific SIRT1 overexpression increases cocaine and morphine conditioned place preference [133]. Similarly, NPAS2 expression is increased in the NAc following repeated cocaine administration which may be important for the rewarding effects of cocaine [19]. Considering NPAS2:BMAL1 may be the primary driver of circadian-dependent gene transcription in the NAc, enhanced drug conditioned reward may rely on NPAS2:BMAL1-mediated transcription (Fig. 1). Thus, cocaine and other drugs of abuse may alter the phase, period, and/or amplitude of molecular rhythms in brain regions including the NAc which has downstream consequences on circadian-dependent signaling pathways.

Circadian regulation of DA biosynthesis and drug reward

The molecular clock regulates local DA synthesis, uptake, and release potentially via the direct transcriptional control of genes encoding major enzymes, transporters, and receptors involved with DA neurotransmission [19,37,136–140]. Identification of binding targets of CLOCK and NPAS2 in the striatum revealed possible novel targets for circadian regulation of DA and GABA neurotransmission in mesocorticolimbic circuitry [19,37]. Many of these targets contain E-Box and/or CRE sites in their promoters, further supporting direct transcriptional control by circadian transcription factors [19,37]. We recently extended these findings by demonstrating NAD^+-and SIRT1-dependent diurnal regulation of DA synthesis and neurotransmission in the mouse VTA [12]. ranscription of the rate-limiting enzyme of DA synthesis, tyrosine hydroxylase (TH), is dynamically regulated by CREB and CLOCK at specific times of day; CREB drives transcription during the active phase (subjective night), while CLOCK recruits SIRT1 during the inactive phase (subjective day) to repress transcription. Recruitment of SIRT1 to the *TH* promoter during the day synchronizes with the peak of NAD^+ abundance, suggesting that diurnal variation of redox state drives time-dependent activity of SIRT1 in the brain. Conversely, disruption of the molecular clock impairs SIRT1 activity and leads to increased TH expression which promotes DA synthesis. These diurnal actions positively associate with time-dependent DA cell firing in the VTA and elevated cocaine conditioned place preference. Pharmacologically increasing NAD^+ availability or restoring SIRT1 activity specifically in the VTA of CLOCK-disrupted (*ClockΔ19*) mice reduces DA synthesis and cocaine-conditioned reward. On the other hand, driving SIRT1 activity and NAD^+ in wild-type mice enhances DA synthesis and neurotransmission, as well as cocaine-conditioned reward, consistent with previous studies showing SIRT1 activation in the NAc promotes cocaine reward [12,133].

Conclusions and Future Directions

Several major pathways of energy production and utilization are under circadian control in the brain. This coupling of circadian pathways to neuronal metabolism may be critical both in maintaining homeostasis as well as optimizing brain energy production and utilization, particularly in the context of drugs of abuse. While the majority of work examining the links between metabolism and circadian regulation has been based in the periphery (*e.g.* liver) or brain areas such as the SCN, it is increasingly evident that these links may be applicable in other brain areas. Indeed, brain regions capable of sustaining high amplitude oscillations may employ rhythmic coupling of astrocyte-neuronal metabolism to tightly regulate activity-dependent neurotransmission [141] – a process that may be critical in mediating the behavioral effects of substances such as cocaine and morphine. We are just beginning to understand the role of astrocyte specific molecular clocks and their role in relevant neural circuits and behaviors [142,143]. Intriguingly, we have recently shown that DA neurons projecting to the NAc from the VTA can tune vesicular DA content and release in response to increases in firing [144]. These neurons concomitantly load DA vesicles with glutamate to facilitate this activity-dependent increase in DA loading and release. Recently, DA neurons from the VTA were shown to project directly to the SCN to resynchronize activity rhythms to photic phase shifting, implying alterations of dopaminergic neurotransmission to NAc may also impact the S N [145]. Further appreciation of subpopulations of midbrain dopaminergic projection neurons may help understand their possible pathway specific involvement in arousal, motivation, and reward [146].

It is also known that diurnal regulation of glutamatergic and dopaminergic neurotransmission within neural circuits related to anhedonia, motivation, and goal-directed behaviors are strongly associated with parallel time-of-day differences in behaviors of conditioned drug reward, drug-seeking and relapse. Drugs of abuse may also entrain cellular and molecular rhythms, leading to the anticipation of subsequent drug administration or drug paired-cue presentations involved in craving and relapse [147,148]. This opens the door to future work exploring whether DA/glutamate co-transmission may be a key process required for the energetic demands of drug-fueled changes in circadian rhythms and neuronal activity associated with reward and addictive behaviors.

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Highlights

- Metabolism and circadian rhythms are intimately connected in brain
- Mitochondrial redox and glycolysis fuel drug-induced neurotransmission
- Rhythmic control of brain energetic pathways is important for drug reward
- Rhythmic NAD+ biosynthesis controls dopamine neurotransmission and drug reward

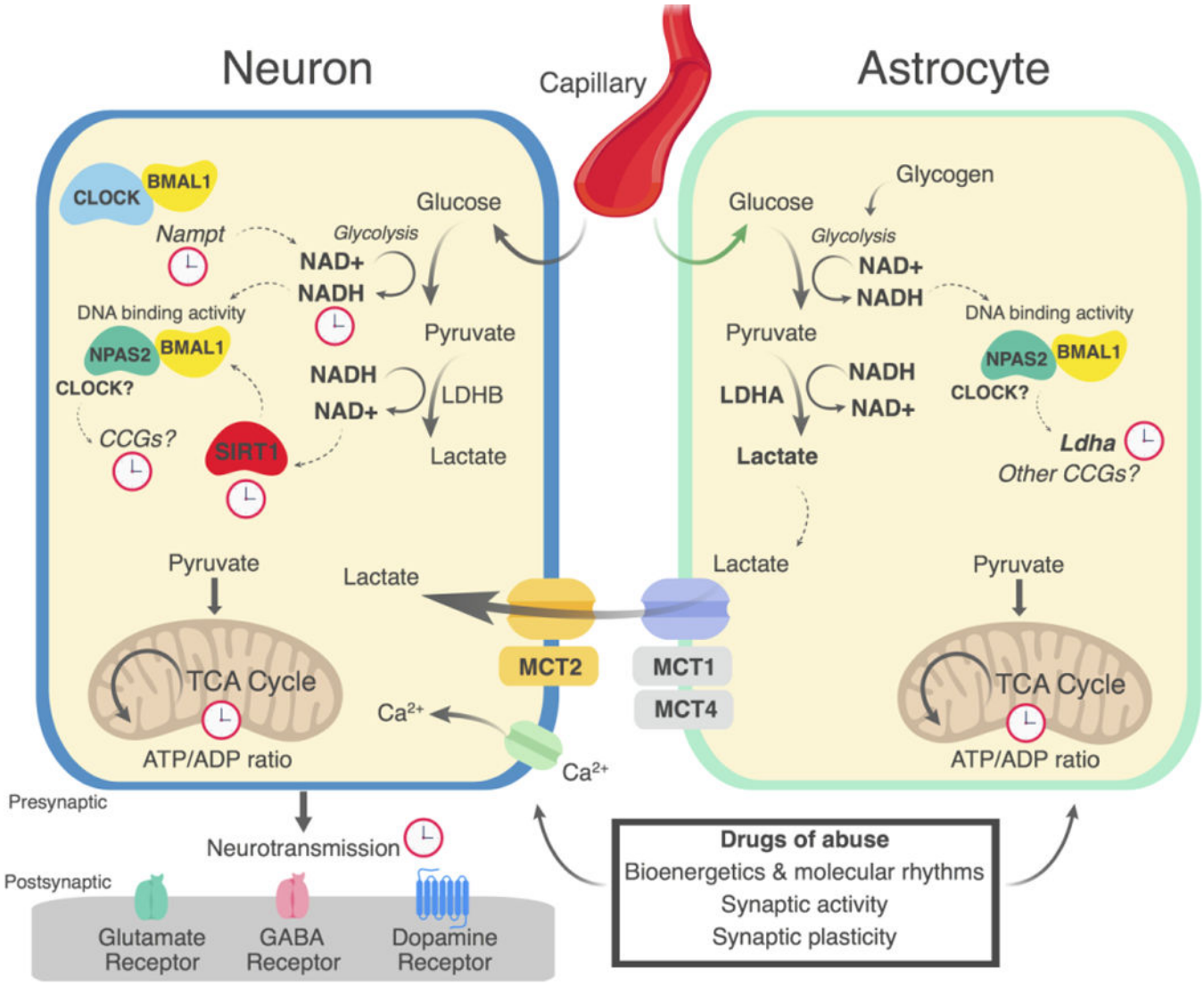

Figure 1.

Proposed model of circadian control of astrocyte and neuronal energetic coupling. Core circadian transcription factors including BMAL1 and CLOCK or NPAS2 regulate the rate-limiting steps of NAD^+ biosynthesis, primarily via the direct transcription of *Nampt*. The DNA binding affinity of CLOCK and NPAS2, BMAL1 dimers is controlled by the intracellular ratio of bioavailable NAD^+ and NADH, where higher NADH tends to enhance the DNA binding activity of the transcriptional complex. The production of lactate through LDHA in astrocytes and LDHB in neurons is critical for elevating intracellular AD^+ levels. NAD^+-dependent deacetylases including SIRT1 is capable of deacetylating BMAL1 or acting on other proteins such as PGC1–03B1 (not shown) to suppress or amplify the transcription of CCGs. Some of these genes encode rate-limiting enzymes necessary for the production of lactate, a major energy substrate for neurons in response to neural stimulation. Glucose is required for glycolysis and conversion of pyruvate to lactate. Lactate is transported from astrocytes by MCT1/4 and into neurons by MCT2. Pyruvate and other energy substrates are used by mitochondria to generate ATP via oxidative phosphorylation.

For example, NPAS2 has been shown to regulate the expression of *Ldha*. These energetic pathways may also be modulated by circadian rhythms in reward-related brain regions, gating the cellular response to drugs of abuse, potentially necessary for drug-induced synaptic and behavioral plasticity.