Neural circuit functions are stabilized by homeostatic processes at long timescales in response to changes in behavioral states, experience, and learning. However, it remains unclear which specific physiological variables are being stabilized and which cellular or neural network components compose the homeostatic machinery. At this point, most evidence suggests that the distribution of firing rates among neurons in a neuronal circuit is the key variable that is maintained around a set-point value in a process called ‘firing rate homeostasis.’ Here, we review recent findings that implicate mitochondria as central players in mediating firing rate homeostasis. While mitochondria are known to regulate neuronal variables such as synaptic vesicle release or intracellular calcium concentration, the mitochondrial signaling pathways that are essential for firing rate homeostasis remain largely unknown. We used basic concepts of control theory to build a framework for classifying possible components of the homeostatic machinery that stabilizes firing rate, and we particularly emphasize the potential role of sleep and wakefulness in this homeostatic process. This framework may facilitate the identification of new homeostatic pathways whose malfunctions drive instability of neural circuits in distinct brain disorders.

The concept of neuronal homeostasis

The concept of homeostasis, based on the classical works of Claude Bernard, Walter Cannon, and James Hardy, refers to the mechanisms that maintain physiological variables within a dynamic range around a ‘set point’ [1–3]. In the context of neural circuits, homeostatic negative feedbacks enable stable activity of neural networks over long timescales, despite the highly dynamic and heterogeneous nature of individual synapses and neurons. Without such homeostatic feedback, the circuit’s function may be destabilized by Hebbian-like synaptic plasticity underlying the cellular basis of learning and memory [4,5]. This plasticity-stability problem has been introduced and elegantly reviewed in earlier insightful papers [6–8], but many key questions remain unanswered. In particular, what are the components of the core homeostatic machinery at the subcellular and neural network levels, and what variable(s) do they regulate to prevent aberrant long-term changes in neural network activity?

The function of many cellular variables such as synaptic weights, ion channels, neurotransmitter release, and receptor expression are dynamic under normal conditions, and scientists are challenged to dissect which of these dynamics are homeostatic in nature. Application of engineering control theory [7] can be used to navigate this issue, based on the following principal characteristics: (i) a set point that the system must return to following a perturbation, which defines the output of the homeostatic machinery; (ii) sensors that detect deviation from that set point; and (iii) homeostatic effectors that precisely retarget some regulated variable to that set point via negative feedback (Figure 1A). Accordingly, when the regulated variable returns to a value close to the set point, all effectors are at minimal or basal levels of activity.

Highlights

- Firing rate distributions and mean firing rate (MFR) present homeostatically regulated variables in central neural circuits.
- Mitochondrial Ca$^{2+}$ buffering is involved in the regulation of the main homeostatic modules underlying firing rate stabilization: set points, sensors, and effectors.
- The core homeostatic machinery can be identified by a dual-challenge approach. Using this framework, the mitochondrial dihydroorotate dehydrogenase (DHODH) enzyme has been uncovered as a regulator of MFR set points in hippocampal networks.
- MFRs and firing rate distributions are homeostatically regulated by sleep in specific neural circuits. As products of DHODH enzymatic activity are inhibited by sleep, DHODH inhibition may mediate a homeostatic decrease of MFRs during sleep.
- Mitochondrial dysfunctions constitute a common hallmark of distinct brain disorders due to a central role of mitochondria in homeostatic firing rate regulation.

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Figure 1. A framework for identifying the members of the core homeostatic machinery essential for mean firing rate (MFR) homeostasis in neural circuits. (A) A classic scheme of a homeostatic controller [7]. In this case, the output of the network is the MFR that is monitored by sensors and maintained at a set-point value by negative feedback mechanisms mediated via effectors. Any deviation from the desired firing rate is sensed as the difference between the desired output (the set point) and the actual output. The error signal is then corrected via the activity of effectors. (B,C) Monitoring the activity of the same neurons for a long time enables testing of whether the MFR in the network is stable. When a constant perturbation (inactivity in B, hyperactivity in C) is introduced to change firing rates (gray arrows), homeostatic mechanisms are activated to adapt the system to the perturbation (adaptation phase). This Type 1 perturbation relates to changes in nonessential (Figure legend continued at the bottom of the next page.)
Here, we focus on the mechanisms that regulate the establishment of activity set points in neuronal networks with particular emphasis on mitochondria. How are set points encoded by neurons and their networks? What are the sensors that detect changes in set point values? How tightly regulated must these values be to prevent neural circuit dysfunction and disease? What mechanisms are in place to encode behavioral state-dependent set points? Addressing these questions is critical for delineating the mechanisms underlying the stability of neural networks.

**Homeostatic regulation of firing rate set points**

The operation of a neuronal circuit depends on the interaction between the intrinsic properties of the individual neurons and the synaptic interactions that connect them into functional ensembles. Despite a large variability in these synaptic and intrinsic parameters, the mean firing rate (MFR) of a neuronal population during ongoing spontaneous activity is typically preserved at a specific set-point value. For instance, the MFR of a neuronal population gradually renormalizes despite the constant presence of a pharmacological, genetic, or experience-dependent perturbation that initially caused a rapid change in MFR (Figure 1B,C). This process dubbed ‘firing rate homeostasis,’ occurs robustly in cultured neural networks ex vivo [9–14], and has been documented in vivo as well, such as in the rodent primary visual cortex (V1) [15–17]. On the basis of these results, MFR can be classified as a physiological variable that undergoes homeostatic set-point regulation.

How does the network’s behavior relate to properties of its single components? Multiple spatial set points may exist, and the specific set point may undergo regulation by homeostatic mechanisms implemented at these various spatial scales [18,19]. In some cases, firing rate homeostasis can be achieved by cell-autonomous mechanisms at the level of single neurons, as in the case of the crustacean stomatogastric ganglion [8] and monocular V1 of rats [20]. Moreover, local homeostatic mechanisms may operate at the level of a dendritic branch to maintain total synaptic strength [21,22] or excitation-to-inhibition ratio [23]. Given a high level of instability of a single neuron firing at long timescales in some neural circuits, such as the hippocampal one [24], additional sensors and effectors may operate globally to stabilize firing at a population level. Indeed, in cultured neural networks, MFR recovery at the population level is more tightly regulated than at the level of single neurons [11,25]. Notably, instability of individual neurons grown in culture is largely intrinsic, as it takes place in a highly controlled environment, regardless of changes in experience, behavioral states, and interactions with higher-order supervising circuits [11]. Large-scale, long-term recordings of firing in different neural circuits with distinct functions in behaving animals will help to determine the scale of firing rate regulation in distinct neural circuits.

In the case of circuit-wide homeostatic regulation, does it involve all cell types? In vivo single-unit recordings in rat V1 show MFR renormalization at the level of regular spiking units (mixed pyramidal neurons and interneurons) and of fast spiking units (mainly attributed to parvalbumin-positive interneurons) during the critical period [15]. By contrast, the same brain area in adult mice shows renormalization of somatic Ca^{2+} rates (reflecting spike rates) in excitatory, but not inhibitory, neurons [17]. Thus, the type of neurons underlying network-level homeostatic MFR recovery may depend on the specific brain region and developmental stage.
A more suitable potential candidate for global stabilization of firing properties at the population level is astrocytes. Astrocytes have emerged as active players in brain energy delivery, production, utilization, and storage [26]. Each astrocyte covers a defined territory with little overlap between neighboring astrocytes, each contacting ~140,000 synapses in the rodent hippocampus [27]. In response to synaptic activity, astrocytes may release gliotransmitters, cytokines, and metabolites that can feed back globally on a large number of synapses and neurons. For example, release of cytokine tumor necrosis factor (TNF)α by glia underlies homeostatic postsynaptic upscaling in response to chronic activity reduction [28]. Moreover, astrocytes are interconnected through gap junctions, forming a large, dynamic network that can sense summed electrical activity across many neurons and elicit a broad feedback response.

There is likely no singular homeostatic effector used to stabilize MFR. Computational work by Eve Marder and colleagues predicted that widely disparate sets of synaptic and intrinsic excitability mechanisms underlie virtually indistinguishable patterns of network activity [8,29]. Synaptic scaling, regulated by the abundance of AMPA receptors at dendritic spines, is one of the most extensively studied homeostatic effectors [9,30], but today a wide repertoire of homeostatic mechanisms has been identified, including changes in synaptic release probability, intrinsic excitability, and excitation-to-inhibition ratio [18,25,31–33]. Furthermore, observation of a specific form of homeostatic plasticity (such as synaptic scaling) alone is insufficient to ensure MFR renormalization following a perturbation. Continuous measurement of a regulated variable such as MFR is essential to determine the sufficiency of specific neural network homeostatic mechanisms.

**Dual-challenge approach for identifying the core homeostatic machinery**

Perturbations to brain activity can be categorized into two classes based on their effects on neural activity. The majority are Type 1; they change MFR only transiently because they do not impair the essential components of homeostatic regulation that cause MFR stabilization (Figure 1B,C). Examples include a constant increase in GABA spillover via inhibition of GABA transporters [11] and a constant increase in glutamate spillover via inhibition of glutamate transporters [13]. These perturbations inhibit and potentiate MFR, respectively, but result in MFR recovery typically after 2 days. By contrast, neural circuits cannot compensate for changes to MFR in the presence of Type 2 perturbations, because they disturb necessary components of the homeostatic machinery. For example, blockade of GABAA receptors impairs MFR compensation to hyperactivity [12], suggesting that GABAA receptors are necessary for homeostatic regulation of MFR.

Discovering Type 2 perturbations that enable persistent changes to MFR will help identify the molecular members of the core MFR homeostasis machinery. Because Type 2 perturbations may target different nodes of the homeostatic machinery, they can only be discovered using a ‘dual-challenge’ approach where they are implemented in conjunction with known Type 1 perturbations that result in adequate compensation of MFR when presented on their own. A Type 2 perturbation that results in a persistent change in MFR without perturbing the homeostatic response to a Type 1 perturbation can be classified as a direct regulator of MFR set point (Figure 1D). In this case, the compensatory mechanisms triggered by the Type 1 perturbation act in reference to a new set-point value. However, if a Type 2 perturbation specifically impairs renormalization of MFR to a set point without affecting MFR on its own, it can be classified as an MFR homeostatic response regulator (Figure 1E), indirectly resulting in a set-point change. Shank3, a postsynaptic density scaffolding protein, is an example of an MFR homeostatic response regulator because its knockdown impairs MFR compensation to inactivity [34]. Thus, the dual-challenge approach enables identification of distinct sources of homeostatic failures.
Physiological regulation of MFR set points by sleep

Vigilance state and firing rate properties covary, which suggests that firing rate homeostasis is state dependent in nature [35,36]. The firing rate of single neurons differs across behavioral states such as active and quiet wake and rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. However, these state transitions affect firing rate differently across brain regions. In sleep-promoting brain areas such as the supraoptic nucleus in the hypothalamus, MFRs are increased during sleep [37]. In some but not all circuits of the neocortex and hippocampus, MFRs decrease during sleep but return to apparent state-dependent set points following transitions into higher vigilance states [38–40]. Notably, MFR is reduced during NREM sleep in deep, but not superficial, cortical layers of V1 [41]. These results suggest that state-dependent mechanisms of MFR homeostasis are inducted locally within neural circuits. Other parameters of firing rate statistics are also hypothesized to be homeostatically regulated by sleep. For example, the distribution of firing rates across neurons in several cortical areas becomes narrower during NREM sleep, displaying a preferential reduction in MFR of highly active neurons alongside an increase in MFR of low-firing neurons [35]. Interestingly, this reflects the change in firing rate distributions in the barrel cortex following whisker deprivation, when homeostatic processes are engaged to stabilize firing after sensory inputs are reduced [42]. These changes to broad network statistics are proposed to coincidentally support plasticity-dependent mnemonic processes and network stability [36], thus solving the ‘plasticity–stability’ problem.

Recent studies suggest that induction of distinct homeostatic mechanisms, such as those that compensate for a constant decrease versus increase in firing rate, occurs in separate vigilance states. Homeostatic MFR recovery in the rodent V1 in response to reduced sensory input (monocular deprivation) occurs during active wakefulness [20], while the homeostatic response to hyperactivity (opening of a closed eye after monocular deprivation) occurs during sleep [43]. As monocular MFR across all the cortical layers is state independent in V1 [15,20], whether similar rules operate in circuits with state-dependent MFR dynamics remains an open question. Specifically, it would be important to demonstrate whether state-dependent MFR set points at the population level are homeostatically maintained following chronic perturbations and whether similar induction rules operate there.

Different homeostatic effectors operate to enable MFR homeostasis across sleep–wake states. Downscaling of excitatory synapses through AMPA receptor removal and shrinkage of spine head volume was identified during normal sleep or recovery sleep following sleep deprivation [44–47]. These results support a hypothesis that sleep induces homeostatic synaptic downscaling to restore the net synaptic strength challenged by synaptic potentiation during wakefulness [44]. However, it is still unknown if total excitatory synaptic strength across a dendritic tree is a regulated variable that is homeostatically maintained or if synaptic scaling of excitatory synapses alone is sufficient for homeostatic recovery of firing rate distributions following a perturbation. In addition to synaptic scaling, sleep deprivation has been shown to increase intrinsic neuronal excitability [48] and augment miniature excitatory postsynaptic current (mEPSC) frequency [49]. This suggests that a decrease in intrinsic neuronal excitability, excitatory quantal synaptic transmission, and excitation-to-inhibition ratio may all contribute to maintenance of lower network MFR set points during sleep.

Sleep pressure represents another physiological variable that is under homeostatic regulation. Since distinct homeostatic mechanisms are induced in sleep and wake states, sleep pressure may serve a role in stabilizing MFR. Sleep homeostasis is reflected by a compensatory increase in sleep duration and in the intensity of sleep, measured as the levels of slow-wave activity during NREM sleep, after extended wakefulness (Box 1). MFR correlates with sleep need in rats [38] and
flies [39], suggesting that this relationship is evolutionarily conserved. However, the relationship between local, state-dependent MFR homeostasis and global sleep homeostasis remains unclear. Recently, global sleep homeostasis has been hypothesized to reflect a spatial integration of local homeostatic processes underlying MFR set-point regulation in distinct circuits [50]. As sleep homeostasis may also occur at the level of local circuits in rats [51] and humans [52], it would be important to test how local perturbations to MFRs in specific circuits affect sleep–wake patterns.

**Mitochondria as homeostatic Ca\(^{2+}\) sensors**

Calcium signaling has long been assumed to play an important role in the homeostatic control of neural activity. Cytosolic Ca\(^{2+}\) (cytoCa\(^{2+}\)) serves as a proxy of spiking activity and is modeled as a feedback control signal [53,54]. According to this model, deviations from a specific target cytoCa\(^{2+}\) value induce transcriptional changes, leading to a precise return of firing properties to a set-point value. Ca\(^{2+}\)-calmodulin-dependent kinases CaMKIV [55,56] and CaMKII [57] have been proposed to sense Ca\(^{2+}\) and to trigger homeostatic changes in synaptic strength in response to a perturbation. CaMKs may be coupled to voltage-gated calcium channels [58,59] or to NMDA receptors [60] to induce a homeostatic response. The role of cytosolic Ca\(^{2+}\) sensors in MFR homeostasis should be further studied. In particular, it remains unknown whether additional Ca\(^{2+}\) sensors are activated by activity changes and participate in firing rate homeostasis.

Calcium homeostasis has been proposed to be a critical module of the core homeostatic machinery underlying MFR homeostasis [61]. Mitochondria are key players in neurometabolism, regulating cellular functions such as respiration and oxidative metabolism. They are also important in calcium homeostasis [62]. Here, we propose that mitochondrial Ca\(^{2+}\) (mitoCa\(^{2+}\)) is maintained at a target level and serves as an error signal in homeostatic MFR regulation. Mitochondria sense two primary consequences of neuronal activity: changes in cytoCa\(^{2+}\) and changes in energy use. This information can then be used to assess and control the MFR set-point value. Ca\(^{2+}\) enters neurons from the extracellular space through voltage-gated Ca\(^{2+}\) channels and NMDA receptors, leading to an increase in cytoCa\(^{2+}\). This triggers Ca\(^{2+}\) uptake by mitochondria via the mitochondrial Ca\(^{2+}\) uniporter (MCU), which functions as the pore of the MCU complex (MCUc) [63]. MCU transcription is homeostatically regulated by long-term changes in activity [64]. MCUc is the macromolecular structure that contains four core
components: the pore-forming MCU protein; the gatekeepers MICU1 and MICU2 or MICU3; and an auxiliary subunit, EMRE, essential for Ca\textsuperscript{2+} transport \[65-69\]. Mitochondria sense changes in Ca\textsuperscript{2+} by Ca\textsuperscript{2+}-dependent activation of MICU, the EF-hand–containing regulatory subunits of MCUc \[63\]. At the ~100 nM resting level of cytoCa\textsuperscript{2+}, MICU1-MICU2 and MICU1-MICU3 heterodimers prevent ion conduction through the MCU channel, and they permit it when Ca\textsuperscript{2+} levels rise \[70\]. While the uniporter becomes activated only when local cytoCa\textsuperscript{2+} levels rise above ~1 μM in non-neuronal cells \[71\], recent work in cultured hippocampal neurons suggests that axonal mitochondria, expressing the brain-specific MICU3 isoform, display higher Ca\textsuperscript{2+} sensitivity \[72\]. MICU3 acts as an enhancer of MCU-dependent Ca\textsuperscript{2+} intake \[73\], while MICU1 acts as an inhibitor at resting conditions \[71,74\] and as a cooperative activator upon Ca\textsuperscript{2+} elevation \[71\]. This Ca\textsuperscript{2+}-dependent activation of MCUc is involved in maintaining physiological mitoCa\textsuperscript{2+} levels in neurons.

It is reasonable to assume that MCUc members may serve as homeostatic Ca\textsuperscript{2+} sensors translating spiking activity to the downstream effectors. Unfortunately, little is known about the molecular composition of MCUc in different types of neurons \[75\] and in distinct neuronal compartments. While MCU was found in both the synaptosome and whole-homogenate fractions of the mouse cortex, MICU3 was detected only in the synaptosome fraction \[76\]. Mitochondria in distinct neuronal compartments may serve different functions. In comparison to synaptic cytoCa\textsuperscript{2+} that serves an adaptive function by activating homeostatic effectors \[12,77,78\], somatic cytoCa\textsuperscript{2+} seems to be a regulated variable, since it is maintained at a target level following visual deprivation in vivo \[16,79\] and pharmacological perturbation in vitro \[11\]. Somatic mitochondria may regulate transcription \[59\], which is required for synaptic scaling \[55\]. However, a recent study suggests that transcription is not required for MFR renormalization, at least for Type 1 perturbations related to hyperactivity \[14\]. Future studies are needed to address whether transcription is unnecessary for inactivity perturbations as well and to understand the role of mitoCa\textsuperscript{2+}–transcription coupling in homeostatic regulation. A recent study suggested that mitochondria decode the intensity of spiking activity \[80\]. In particular, the authors demonstrated loose coupling between mitoCa\textsuperscript{2+} and cytoCa\textsuperscript{2+} such that mitochondrial calcium events are mainly associated with high-frequency spike bursts in the neocortex of behaving mice. Thus, somatic mitochondria may efficiently encode high-frequency spike bursts and thus play a critical role in synaptic plasticity and information encoding \[81\]. Indeed, MCU has been recently demonstrated to regulate synchronization of network activity \[82\].

Finally, whether MCUc is the only complex participating in mitoCa\textsuperscript{2+} uptake in neurons remains an open question \[83\]. The source of Ca\textsuperscript{2+} influx to mitochondria may also differ between cell types and subcellular compartments. While reliance of non-neuronal cell types on endoplasmic reticulum (ER)-Ca\textsuperscript{2+} as a mitochondrial source is well documented \[83,84\], in neurons, the situation seems to be more complicated. For example, dendritic mitochondria have been suggested to use the ER as a Ca\textsuperscript{2+} source \[85\], whereas axonal mitochondria do not rely on the ER as a source of Ca\textsuperscript{2+} uptake \[72\]. This may be explained by differences in the proximity of mitochondria and the ER, in the MICU subunit composition and their Ca\textsuperscript{2+} affinity, or by differences in mitochondrial morphology in axons and dendrites. Identification of the exact molecular mechanisms regulating mitoCa\textsuperscript{2+} at the somatic compartment remains an exciting topic for future investigation.

**Ca\textsuperscript{2+} buffering by mitochondria as a homeostatic effector**

Mitochondria may participate in a wide repertoire of adaptive mechanisms underlying MFR homeostatic recovery to a perturbation. Namely, partial mitochondrial uncoupling impairs MFR normalization \[13\]. What are the molecular mitochondrial mechanisms that mediate MFR homeostatic response to a perturbation? Mitochondrial uncoupling causes a decrease in resting mitoCa\textsuperscript{2+} and mediates presynaptic effects of the insulin-like growth factor 1 receptor on spontaneous and
evoked neurotransmission [86]. Notably, presynaptic effects of mitochondria depend on its localization, regulated by Miro1 [87]. Presynaptic Ca2+ signals, as well as neurotransmitter release, are significantly lower in terminals containing mitochondria [88,89]. Moreover, the localization of mitochondria at presynaptic sites and presynaptic plasticity can be homeostatically altered during long-term activity changes via Miro1 [89]. Notably, these presynaptic changes are mediated by MCU [88,89] that may serve as a mitochondrial homeostatic effector. An additional possible molecular effector in mitochondrial control of MFR homeostasis is the mitochondrial fission factor, which negatively regulates the size of mitochondria entering the axon, thus adjusting the capacity for presynaptic calcium buffering and neurotransmission [90]. At the postsynaptic site, dynamin-like GTPases Drp1 and OPA1 may serve the function of homeostatic effectors by maintaining the dendritic mitochondria content and dendritic spine density [91]. Finally, Ca2+ buffering by mitochondria may alter the intrinsic excitability of neurons. For example, diet-induced obesity causes a decrease in excitability of satiety-mediating hypothalamic pro-opiomelanocortin (POMC) neurons by impairing mitoCa2+ handling [92].

In comparison to somatic mitochondria, axonal and dendritic mitochondria play an important role in compensatory mechanisms by regulating local translation [93,94]. While translation is known to play an important role in homeostatic synaptic scaling [85], future studies are needed to understand how transcriptional and translational mechanisms are regulated by mitochondria to coordinate homeostatic changes in different neuronal compartments to enable MFR set-point stabilization.

It is important to emphasize that it is still unknown which of the aforementioned mitochondrial signaling molecules may be involved in inducing a typical homeostatic compensation (Type 1 perturbation; Figure 1B,C) and which are essential for MFR homeostasis (Type 2 perturbation; Figure 1C,D). Of the aforementioned molecules, only Miro1 has been directly linked to homeostatic presynaptic plasticity so far [89]. An exciting question is whether presynaptic homeostatic plasticity is sufficient for a circuit-wide MFR homeostatic recovery. Future studies are needed to test the role of specific mitochondrial signaling molecules in MFR homeostasis.

**Mitochondrial DHODH as a homeostatic regulator of firing rate set points**

Using an unbiased computational approach based on genome-scale metabolic modeling, the mitochondrial dihydroorotate dehydrogenase (DHODH) enzyme has been identified as a modifier of metabolic homeostasis in hippocampal and cortical circuits [13]. DHODH is located in the inner membrane of the mitochondria and links two major intracellular processes: the fourth reaction of de novo pyrimidine biosynthesis and electron transfer from dihydroorotate to ubiquinone as part of the mitochondrial electron transport chain [96] (Figure 2A). On the basis of electrophysiological, optical, and metabolic measurements, DHODH has been identified as a regulator of MFR set points in hippocampal networks [13] (Figure 2B). Constant DHODH inhibition by the specific blocker trifluoromide induces a stable suppression of MFR in cultured hippocampal networks and in the CA1 hippocampal circuitry of behaving mice. Notably, no sign of homeostatic compensation was observed during 2 days of recordings as is expected for a typical Type 1 perturbation [11]. Furthermore, DHODH suppresses MFRs without impairing homeostatic compensation in response to a perturbation. These data implicate DHODH as a homeostatic set-point regulator but not as an MFR homeostatic response regulator, indicating that these two processes are separately regulated. DHODH inhibition lowers MFRs by suppressing intrinsic neuronal excitability and excitatory quantal synaptic transmission. At the cellular level, DHODH inhibition inhibits resting mitoCa2+, while it increases mitoCa2+ evoked by spike bursts [13]. Importantly, DHODH inhibition did not decrease ATP production and did not limit the maximal neuronal firing, despite a decrease in spare respiratory capacity of the mitochondria [13]. Moreover, the persistent effect of DHODH inhibition on MFRs did not depend on uridine [13], implying that the products of de novo pyrimidine
(A) Glutamine + HCO₃⁻ + ATP → Dihydroorotate → Orotate → Uridine

(B) DHODH inhibition

Mitochondria
- Decreased resting mitoCa²⁺
- Increased evoked mitoCa²⁺
- Decreased mitochondrial respiration

Neuron
- Decreased intrinsic neuronal excitability
- Decreased excitatory quantal synaptic transmission

Neural network
- Decreased MFR of neural networks
- Preserved homeostatic response to a perturbation

(See figure legend at the bottom of the next page.)
Regulation of DHODH enzymatic activity by vigilance states

What are the physiological regulators of DHODH activity? A recent metabolomic study in mice revealed 11 cortical metabolites that are present at significantly higher levels during awake than in sleep states; this was shown during baseline and after extended wakefulness [97]. While some metabolites, such as lactate and pyruvate, were previously shown to be regulated by sleep–wake states [98–102], other metabolites were novel in this context. To our surprise, one of them was orotate, a direct product of oxidation of dihydroorotate by the mitochondrial DHODH enzyme. The concentration of orotate was higher during wakefulness and lower during sleep and positively correlated with the electroencephalogram (EEG) slow-wave activity (reflecting sleep need) in the medial prefrontal cortex [97]. These data indicate that DHODH activity is inhibited during sleep, thus producing less orotate from dihydroorotate. According to this hypothesis, the concentration of dihydroorotate (DHODH substrate) is expected to show an opposite relationship to sleep–wake states in comparison to orotate. Interestingly, in addition to orotate, the concentration of uridine, the end product of a de novo pyrimidine synthesis pathway, is also decreased during sleep and correlated to the EEG slow-wave activity during recovery sleep [97]. However, the interpretation of uridine results is less straightforward, since uridine concentration depends on both de novo synthesis and the salvage pathway. Thus, regulation of orotate concentration by sleep–wake states and sleep pressure strongly indicates that it is the enzymatic activity of DHODH which is regulated by vigilance states, being activated by an increase in sleep need.

Prediction: sleep inhibits firing rates via DHODH

On the basis of the aforementioned metabolomic and electrophysiological studies, we propose that the mitochondrial DHODH enzyme may play a critical role in homeostatic regulation of MFR set points by sleep (Figure 3). With the use of basic concepts of control theory, these predictions can be tested experimentally to address the validity of the proposed hypothesis. Sleep is expected to cause DHODH inhibition, increasing mitoCa$^{2+}$ buffering during spiking activity and resulting in a decrease to MFR [13]. Thus, basal DHODH activity may contribute to the maintenance of MFR set points during active wake states, while DHODH inhibition may contribute to MFR suppression during sleep. Moreover, the degree of DHODH inhibition is expected to depend on sleep pressure. Interestingly, sleep deprivation decreases circadian changes in MCU phosphorylation in mouse forebrain synaptoneurosomes [103]. Future studies are needed to test whether MCUc mediates the DHODH effect on mitoCa$^{2+}$ and MFR during the sleep–wake cycle.

In addition to regulating DHODH activity, the transition from wakefulness to sleep is associated with diverse metabolic changes, including decreased cerebral metabolic rate of oxygen [104] associated with reduced MFRs [105], decreased cerebral glucose metabolism [102], higher oxidative phosphorylation as evident by decreased lactate levels [98–102], activity-dependent
changes in the concentration of extracellular ions (K⁺, Ca²⁺, and Mg²⁺) [106], and facilitated metabolite clearance [107] due to structural and metabolic changes in the brain [108]. Moreover, mitochondrial reactive oxygen species promote sleep in flies by inactivating A-type potassium currents [109]. These may be additional players impacting MFR set-point regulation by sleep.

**Homeostatic dysregulation of firing rate set points in distinct brain disorders**

We propose that mitochondrial dysfunctions constitute a common hallmark of distinct brain disorders due to the central role of mitochondria in homeostatic firing rate regulation. A wide range of brain disorders are associated with abnormal firing rates and patterns in specific microcircuits or multiple interacting circuits. While impairments of homeostatic control have been suggested to drive neurodegenerative [61,110], neurodevelopmental [111,112], and psychiatric [113] disorders, it is unknown how homeostatic dysregulation of firing rate set points contributes to the progression of these disorders. Homeostatic set points may be dysregulated under pathological conditions, such as intractable epilepsy [13] and Alzheimer’s disease [110]. Integration of experimental and theoretical approaches is crucial for understanding the principles and mechanisms that disrupt stability at the cellular and network levels. Distinctions between mitochondrial mechanisms underlying pathogenic versus compensatory pathways and between the sources of homeostatic failures are essential for the proper design of treatment strategies. Chronic homeostatic disorders may result from locking the system in a stable pathological state, being detrimental for circuits' functioning.
As a result, all the compensatory mechanisms start acting in reference to this pathological set-point value. Thus, therapeutic approaches at the level of homeostatic feedback responses might be ultimately ineffective or even aversive if pathological firing properties are caused by malfunction of set points.

Concluding remarks
Recent studies highlight mitochondria as central players in the stabilization of basic neural circuit functions. Despite significant progress in the field of neuronal homeostasis, many questions remain open (see Outstanding questions). Addressing these questions is critical to determine whether and how mitochondrial signaling pathways regulate firing rate homeostasis in specific brain microcircuits and their functions. Furthermore, whether deficits in these pathways drive pathogenesis in brain disorders associated with aberrant spiking activity remains to be determined.

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The authors declare no competing interests in relation to this work.

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Outstanding questions
Does preservation of the circuit-level MFR via reorganization of its inputs affect network performance? Does the precise mechanism(s) of MFR compensation matter? What is the magnitude of MFR over- or undercompensation that results in network dysfunction?

How do mitochondria sense changes in spiking activity to guide a precise feedback control of MFR? Does mitoCa2+ regulate MFR homeostasis by encoding high-frequency spike bursts? Which mitochondrial signaling pathways directly regulate MFR set-point versus homeostatic feedback response?

Are glial cells involved in homeostatic regulation of MFRs at the network level? If so, what are the specific functions of astrocytes and microglia? How do astrocytic mitoCa2+ and intercellular mitochondrial transfer between astrocytes and neurons affect MFR stabilization at the network level?

What are the signaling pathways that transduce changes in the extracellular environment to mitochondrial DHODH activity in neurons? What are the molecular mechanisms underlying MFR set-point regulation by DHODH?

What are the mitochondrial mechanisms that regulate MFR by sleep in specific neural circuits? Does DHODH enzymatic activity regulate sleep homeostasis?

What are the neuromodulators that activate DHODH during wakefulness?
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