Homeostatic control of neuronal activity

Drion, Cato

Published in:
Recent Advances in Homeostasis

DOI:
10.5772/intechopen.108577

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,500
Open access books available

175,000
International authors and editors

190M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter

Homeostatic Control of Neuronal Activity

Cato Drion

Abstract

For healthy brain functioning, it is crucial that neuronal networks do not become hyperactive, but also, that they remain excitable. Homeostatic mechanisms ensure that neuronal activity remains within a functional range. How does that work? In this chapter, we will explore homeostatic control of neuronal activity. We will start by introducing the basics of neuronal communication to establish what makes a neuron excitable. Then, we will learn how neurons are able to tune their own excitability, which is called homeostatic intrinsic plasticity. Next, we will discuss the ability of neurons to tune the strength of their connections to other neurons. This is called homeostatic synaptic plasticity and involves synaptic scaling, the up- and downregulation of receptors, and the control of neurotransmitter release. Finally, we will review the role of glia in neuronal network homeostasis and discuss disorders where the homeostatic control of neuronal activity is compromised.

Keywords: neuronal excitability, homeostatic intrinsic plasticity, homeostatic synaptic plasticity, synaptic scaling, neurotransmitter release, receptors

1. Introduction

All our thoughts, feelings, and actions are enabled by the cells of our nervous system: neurons. Neurons communicate with each other and with the rest of our body, our organs, senses, and muscles. Neuronal activity is essential to function, but at the same time, neuronal activity should not become excessive. To understand how neuronal activity is under homeostatic control, we first need to understand the basics of neuronal activity.

1.1 The electrochemical basics of neuronal activity

Neurons communicate via electrochemical signals. They pass on currents to one another through the extracellular space and across the neuronal cell membrane. These currents are carried by ions, primarily sodium (Na$^+$), potassium (K$^+$), and chloride (Cl$^-$), that can pass the neuronal membrane through specialized pores: ion channels. Neurons can communicate this way because they are electrically charged: there is a difference in charge between the extracellular and intracellular space, called the membrane potential. At rest, the membrane potential of a neuron is about $-70$ millivolts (mV). From this baseline value, the neuron can either depolarize (the membrane...
potential becomes less negative) or hyperpolarize (the membrane potential becomes even more negative), depending on what messages the neuron receives. To be able to receive and respond to these changes in membrane potential, a neuron needs to maintain a stable resting membrane potential.

The membrane potential depends on the distribution of ions across the neuronal membrane. Therefore, it is crucial that the concentrations of ions in the intracellular and extracellular space are tightly regulated. Part of this is done by transporters that actively carry ions in and out of the cell. The most important transporter continuously exchanges three Na\(^{+}\) ions for two K\(^{+}\) ions and is therefore called the sodium-potassium pump. But also, glial cells play an important role herein. Astrocytes, for instance, buffer K\(^{+}\) ions and ensure that ions are distributed across neuronal networks. These examples illustrate how neurons maintain a stable baseline, when they are at rest. But what happens during neuronal activity?

If an incoming signal from the environment (another neuron, for example) triggers a strong enough depolarization, a neuron can generate action potentials, which are the “messages” neurons send to one another. An action potential is a short, transient, and high-amplitude depolarization of the membrane potential, which only occurs if the membrane potential surpasses a threshold value. This has everything to do with the type of ion channels involved: voltage-gated ion channels.

Voltage-gated ion channels only open when the membrane potential is between specific values. They also close at specific values, creating a limited window for ions to cross the membrane. This ensures that the membrane potential can be restored to baseline values after neuronal activity. In addition, the currents carried by specific ions also behave in a voltage-dependent way. In general, Na\(^{+}\) will only flow into a neuron (thereby generating a positive inward current that depolarizes the membrane potential) if the membrane potential is negative. K\(^{+}\), on the other hand, is more inclined to leave the neuron (thereby generating a positive outward current that hyperpolarizes the membrane potential) if the membrane potential is positive. How much of a particular ion can cross the membrane, and thus, how much current it can generate, depends on the amount of open ion channels. This is then dependent on the membrane potential, but also on the amount of ion channels available. As we will see in this chapter, neurons can regulate the amount of voltage-dependent ion channels available in the membrane. To summarize, the membrane potential, the distribution of ions, and the amount of voltage-gated ion channels all determine whether or not a neuron will generate an action potential (Table 1).

How well a neuron is capable of generating an action potential reflects its excitability. It is crucial that neuronal excitability remains within limits; it should not be too hard, but also not too easy, for a neuron to fire an action potential. Several mechanisms contribute to keeping neuronal excitability within limits, as we will see later on. First, we will discuss how an action potential is transmitted from neuron to neuron—in other words: how do neurons talk to each other?

1.2 The synapse

The site where neurons connect, and electrochemical signals are being transmitted from one neuron to another is called the synapse (Figure 1). In the most common type of synapse, the transmission happens from the axon terminals of the presynaptic (“sending”) neuron to the dendritic spines of the postsynaptic (“receiving”) neuron. Transmission of the electrochemical signals across the synapse usually requires the presynaptic neuron to release a neurotransmitter at its axon terminal. A neurotransmitter is a
Homeostatic Control of Neuronal Activity
DOI: http://dx.doi.org/10.5772/intechopen.108577

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ions</td>
<td>Charged particles: sodium (Na⁺), potassium (K⁺), chloride (Cl⁻) and calcium (Ca²⁺) are important</td>
</tr>
<tr>
<td>Membrane potential</td>
<td>The difference in charge between the intra- and extracellular space</td>
</tr>
<tr>
<td>Action potential</td>
<td>A rapid, high-amplitude depolarization of the membrane potential that can be passed on to neighboring neurons and thus serves as a “message”</td>
</tr>
<tr>
<td>Neuronal excitability</td>
<td>How easily can a neuron be prompted to generate an action potential?</td>
</tr>
<tr>
<td>Voltage-gated ion channels</td>
<td>Channels that open, close, and inactivate in response to changes in the membrane potential</td>
</tr>
</tbody>
</table>

Table 1. Important definitions in neuronal activity.

Figure 1. (created with BioRender.com): the biochemical basis of neuronal communication. A simplified drawing of the typical chemical synapse. (1) In the presynaptic neuron, an action potential arrives at the axon terminal, where it triggers calcium (Ca²⁺) influx. (2) Ca²⁺ triggers the fusion of neurotransmitter-containing vesicles with the neuronal membrane and consequently, neurotransmitter is released into the synaptic cleft. (3) The neurotransmitter binds to the receptors on the dendritic spine of the postsynaptic neuron. This will—either directly or indirectly—cause ions to flow across the postsynaptic membrane (4) and thereby change the membrane potential (4) —a postsynaptic potential (which can be either inhibitory or excitatory) is created. Following neuronal activity, a number of processes help to restore activity levels. (5) The sodium-potassium pump exchanges three sodium (Na⁺) ions for two potassium (K⁺) ions to restore or maintain constant ion distributions. Neurotransmitters are degraded, taken up by the presynaptic neuron or (6) bind to presynaptic autoreceptors that regulate neurotransmitter release. (7) Glia take up neurotransmitters and ions.
signaling molecule that usually binds as a ligand for a specific receptor. Neurotransmitter release is initiated by a signal from another important ion: calcium (Ca\(^{2+}\)). While the other cations (Na\(^{+}\), K\(^{+}\)) are the most important players in the membrane potential and the action potential, Ca\(^{2+}\) acts as a signaling molecule in all kinds of intracellular chain reactions. In the presynaptic axon terminal, the chain reaction starts when an action potential arrives there (the presynaptic neuron “fires”). The action potential depolarizes the membrane potential, which opens voltage-gated Ca\(^{2+}\) channels. This triggers Ca\(^{2+}\) influx into the axon terminal, which in turn causes neurotransmitter-containing vesicles to fuse with the presynaptic membrane and release the neurotransmitter into the synaptic cleft. There, neurotransmitter molecules bind with their receptors on the postsynaptic neuron. The receptors then get activated and either directly or via second messengers, allow ion channels to open, which causes ions to flow through and change the postsynaptic membrane potential: the electrochemical message has been received.

Remember that the ion channels in this description are (either directly or indirectly) operated by receptors that are activated by neurotransmitters. We call those channels “ligand-gated” ion channels (see Figure 1).

Excitatory neurons send an activating message: they release neurotransmitters that induce a depolarization of the postsynaptic neuron. The most important excitatory neurotransmitter is glutamate. Glutamate is a ligand for glutamatergic receptors such as the AMPA receptor (AMPA-R) and the NMDA receptor. Throughout this chapter, we will repeatedly encounter the AMPA-R in homeostatic processes. The AMPA-R is a ligand-gated ion channel: when glutamate binds to the AMPA receptor, the conformation of the receptor changes and this allows Na\(^{+}\) to enter the neuron. The entry of Na\(^{+}\) depolarizes the membrane potential, we call this an excitatory postsynaptic potential (EPSP).

Inhibitory neurons release neurotransmitters that result in a hyperpolarization of the membrane potential of the postsynaptic neuron; they generate inhibitory postsynaptic potentials (IPSPs). For example, their receptors will allow anions (negative ions, here: Cl\(^{-}\)) to enter the neuron, or allow potassium (K\(^{+}\)) ions to leave the cell. Both mechanisms hyperpolarize the cell, making it more difficult to generate an action potential. Table 2 lists the most important terms in synaptic transmission.

Neurons make many connections with neighboring neurons: they form neuronal networks. A neuron can have thousands of synapses, and hence, receives synaptic input from a large number of excitatory and inhibitory numbers, in other words: it gets messages to tell it to fire, but at the same time, surrounding neurons may send messages to prevent the firing. For neuronal functioning, it is important that the balance between excitatory input and inhibitory input is maintained, within the neuron (the amount of inhibitory and excitatory synapses), but also at the network level (the amount of inhibitory and excitatory cells in a network). We will see that this balance between excitation and inhibition is under homeostatic control. To understand how this happens, we must first introduce neuronal plasticity.

### 1.3 Neuronal plasticity

Neuronal networks are not static—in fact, the connections within a neuronal network change all the time. This high degree of plasticity has been primarily demonstrated in brain areas associated with learning and memory, and indeed, it seems to underlie our ability to learn.

In 1949, the Canadian psychologist Donald Hebb proposed that if one neuron repeatedly fires together with another neuron, the connection between those neurons will be reinforced. The phrase “neurons that fire together, wire together” is
often used to illustrate this structural plasticity that we still call Hebbian Learning. Hebbian learning is a form of structural synaptic plasticity: the shaping of connections between neurons occurs by strengthening or weakening specific synapses. We will briefly illustrate how this works, so we can compare and contrast the underlying mechanisms to homeostatic synaptic plasticity later on.

Repeated simultaneous activation of a pre- and postsynaptic neuron will trigger the influx of Ca^{2+}, not only at the pre-synapse (remember how Ca^{2+} influx initiates presynaptic neurotransmitter?) but also in the postsynaptic cell. Here, Ca^{2+} can enter the cell through voltage-gated Ca^{2+} channels and NDMA receptors, but Ca^{2+} is also released from intracellular stores in response to stimulation. The activity-dependent rise in intracellular Ca^{2+} triggers specialized proteins to take action: they are Ca^{2+}-dependent kinases (CaMK) that phosphorylate other proteins and thereby trigger intracellular processes. In this case, consider CaMKII: this kinase phosphorylates subunits of the AMPA receptors, making those more active. Furthermore, Ca^{2+} will set off signaling cascades resulting in the synthesis of proteins that enhance synaptic transmission, for example, extra receptors, or the building blocks of those receptors (subunits). Or, proteins are produced that transport additional receptors and insert them into the membrane, or proteins that keep the receptors “trapped” in the membrane (these are called postsynaptic density proteins). In addition to protein synthesis, the signaling cascades can also stimulate the formation of contact points (postsynaptic dendritic spines) between neurons.

These processes collectively make the postsynaptic neuron more responsive and thus, strengthen the connection at that specific synapse. The next time this synapse gets stimulated, its response will be stronger. This is a long-lasting effect (up to months in the rodent hippocampus) and hence we call this long-term potentiation (LTP) [1]. The counterpart of LTP is called long-term depression (LTD), which happens at synapses that are not used enough: these connections are weakened or even removed. Hebbian learning occurs through enhancing the relevant connections with LTP and removing the irrelevant ones through LTD, thus shaping the brain through experience. We will later refer to this as “Hebbian plasticity.” Of note, the example mechanisms described here are not all there is to it. For instance, you may have noticed that we have discussed post-synaptic LTP mechanisms only, but there are also—albeit less (known) mechanisms taking place in the pre-synapse.

Table 2. Important definitions in synaptic transmission.

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synapse</td>
<td>Contact point between neurons, where signals are sent presynaptically and received postsynaptically</td>
</tr>
<tr>
<td>Axon</td>
<td>Protrusion from the neuron that conducts signals from the cell body to the synapse (“sending”)</td>
</tr>
<tr>
<td>Dendrite</td>
<td>Protrusion from the neuron that conducts signals from the synapse to the cell body (“receiving”)</td>
</tr>
<tr>
<td>Ligand-gated ion channel</td>
<td>Ion channel that is activated when a ligand binds to it, or when a ligand binds to the receptor that indirectly activates it</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Signaling molecule that enables synaptic signaling by binding to the receptor for which it is the ligand</td>
</tr>
<tr>
<td>Receptor</td>
<td>Protein that binds neurotransmitters, which then triggers a response in the receiving neuron</td>
</tr>
</tbody>
</table>

---

*Homeostatic Control of Neuronal Activity*

DOI: http://dx.doi.org/10.5772/intechopen.108577
Now you know the basics of neuronal activity and neuronal plasticity, we will dive into homeostatic control of neuronal activity.

2. Homeostatic control of neuronal activity

In the brain, there is a high degree of plasticity. Neuronal networks shape their connections according to experience, and this underlies our ability to learn. Neurons are able to selectively strengthen and weaken their synapses, which reinforces their excitability. However, neurons should not become too easy to excite: hyperexcitable neurons lose the ability to respond selectively to relevant inputs, which disables normal functioning. Furthermore, as we will see later on, the hyperexcitability of neuronal networks can lead to epilepsy. But it should also not become too hard to excite a neuron: without responsive neurons, neuronal networks would fall silent. Thus, the excitability of neurons and neuronal networks needs to be kept within functional limits. In the healthy brain, neurons compensate for hyperactivity or lack of activity using several mechanisms. These mechanisms aim to restore excitability to baseline levels and keep activity of neuronal networks within limits. In other words, these mechanisms constitute homeostatic control of neuronal activity.

In this chapter, we will explore the mechanisms of different types of homeostatic plasticity. Homeostatic plasticity can be divided into two categories: homeostatic intrinsic plasticity and homeostatic synaptic plasticity. The latter pertains to mechanisms influencing connections between neurons, mostly targeting the functioning of ligand-gated ion channels and neurotransmitters. Homeostatic intrinsic plasticity concerns a neuron's own baseline level of excitability. This type of homeostatic plasticity mostly concerns voltage-gated ion channels, as we will discover in the next section.

2.1 Homeostatic intrinsic plasticity

Different types of neurons usually have their own typical pattern of activity: specific characteristics that are called intrinsic firing properties. Intrinsic firing properties are genetically imprinted during the early stages of neurodevelopment, by the expression of specific transcription factors. Examples of these intrinsic firing properties are: how difficult or easy it is to generate an action potential (the threshold), how often the neuron can generate consecutive action potentials (the firing frequency range), what currents specifically play a role in the action of this neuron (depending on what type of ion channels the neuron expresses) et cetera. Intrinsic firing properties dictate the typical behavior of a neuron and are used to discriminate between types of neurons.

Interestingly, the fact that these intrinsic firing properties are fixed does not mean that there is no room for plasticity: rather than one value for each property, intrinsic firing properties are defined as a range, and within that range a neuron can adapt its behavior. This means that within certain limits, a neuron can use cellular mechanisms to adjust its excitability. This is what happens in homeostatic intrinsic plasticity.

Homeostatic intrinsic plasticity is simply put: neurons sensing their own excitability and consequently adjusting it in a compensatory manner. For example, if a neuron has been inactive for a while, it will increase its responsiveness to subsequent input, as if to become more sensitively tuned to incoming signals. Conversely, if a neuron has been increasingly active previously, it is able to decrease its output in response to later input. How does a neuron do this?
In the introduction, we have seen that the excitability of a neuron depends on, among other factors, how many voltage-gated ion channels are expressed in the membrane. Mainly the voltage-gated Na\(^+\), K\(^+\), and Cl\(^-\) ion channels play a role in generating action potentials. To make a neuron depolarize (and thus make it more likely to fire, or enhance excitability), the Na\(^+\) channels are important, whereas the K\(^+\) and Cl\(^-\) channels tend to hyperpolarize the membrane potential of a neuron (and thus make it less likely to fire). You could simplify this by saying that in most cases, Na\(^+\) channels are excitatory, K\(^+\), and Cl\(^-\) channels are inhibitory.

Interestingly, it was shown that neurons can adapt the amount of voltage-gated ion channels in the membrane, depending on external input. This was demonstrated with electrophysiological recordings of isolated neurons in vitro: single neurons were isolated in a petri dish, and their activity was recorded with an electrode. Without a surrounding neuronal network, the neurons did not receive any synaptic input. The experimenters call this “chronic inhibition” (Figure 2) to indicate that neuronal activity was inhibited for a longer period of time. When the researchers probed the neuron (gave a stimulus), the isolated, chronically inhibited neurons were silent at first. But after a couple of days, the neurons became more active: the experimenters found that there were more excitatory ion channels expressed in the membrane after a couple of days.

![Figure 2](created with BioRender.com): the effect of chronic inhibition in isolated neurons in vitro. Under normal conditions, there is a balanced expression of inhibitory (orange) and excitatory (purple) voltage-gated ion channels. Following prolonged inhibition, the expression of excitatory ion channels is enhanced, and that of inhibitory ion channels reduced. Based on experiments described in [2, 3].
days in vitro, and less inhibitory channels. Also, the responsiveness of these ion channels was altered. Together this led to enhanced activity (more action potentials) of the neuron. So although initially the neurons were silent, their excitability increased again, until the level of excitability that is typically seen in that type of neuron under normal conditions (within a neural network) [3]. Importantly, when the experiments were repeated but the activity of Ca^{2+} was blocked, neurons were no longer able to do this. Apparently, individual neurons restore their excitability by using a calcium-dependent mechanism to adjust their voltage-gated ion channel expression (see Figure 2 for a simplified schematic illustration of this process).

We have now seen an example of how neurons can restore their baseline activity levels by altering their voltage-gated ion channels. In addition to inserting more of a specific ion channel into their membrane, as we have just discussed, a neuron has other options, for example: making an ion channel more or less prone to open at certain membrane voltages by changing the composition of an ion channel. It was also shown by several studies that neurons compensate for the loss of function of one type of ion channel by inserting another type of channel with a similar function, to restore their intrinsic firing properties. These are all forms of “rebalancing ion channel distribution” (reviewed in [2]) that aim to restore the characteristic intrinsic firing properties of a neuron. The fact that a neuron is doing this, even when it is isolated in a petri dish, indicates that these firing properties must be somehow encoded genetically. This enables, but also drives a neuron to always restore its excitability to a “baseline” level.

Further, studies have shown that a neuron can move or adjust the size of its axon initial segment, which is the area at the beginning of an axon where a neuron generates its action potential. How far the axon initial segment is from the cell body (soma) is an important determinator for the excitability of a neuron (see [4]). Research has shown that in response to excessive input, neurons can move the axon initial segment away from the soma [5]. This too is a calcium-dependent process, and the consequence is an increased threshold to generate an action potential. Note that the reverse is also thought to be possible [6].

We have now seen a couple of examples of mechanisms in homeostatic intrinsic plasticity. It is not necessary for a neuron to receive synaptic input to trigger these mechanisms. Rather, they are driven by the membrane properties of the neuron itself. That is why it is called homeostatic intrinsic plasticity. Calcium plays an important role in homeostatic intrinsic plasticity, but the exact mechanisms through which this all happens remain to be unraveled. For homeostatic synaptic plasticity, however, the underlying processes have been identified in a bit more detail, as we will see in the next section.

2.2 Homeostatic synaptic plasticity

In the previous section, we have seen that neurons use homeostatic intrinsic plasticity to regulate and restore their own, intrinsic activity levels, mostly by tuning their voltage-gated ion channels. Next, we will explore homeostatic synaptic plasticity mechanisms that, as the term suggests, involve synaptic effectors: ligand-gated ion channels, neurotransmitters, and their receptors.

2.2.1 Postsynaptic regulation of receptors and synaptic scaling

In addition to their voltage-gated ion channels, neurons are also known to tune their ligand-gated ion channels and neurotransmitter receptors in response to
network activity. You may remember reading something similar in the introduction of this chapter, where the cellular mechanisms behind Hebbian learning were briefly discussed. Like Hebbian plasticity, homeostatic synaptic plasticity involves inserting or removing receptors to and from the membrane. But in contrast to Hebbian plasticity, the effect is not reinforcing the input a neuron receives, but rather, counterbalancing it. It might seem that Hebbian and homeostatic synaptic plasticity are opposing each other—but luckily, homeostatic mechanisms do not interfere with learning, as we will see next.

As you may recall, LTP and LTD are synapse-specific processes. In contrast, homeostatic synaptic plasticity can up- or downregulate the excitability of the whole neuron at once. This explains why homeostasis does not prevent learning: if the overall excitability of the neuron is in- or decreased, the relative strength of individual synapses is unaffected. The first type of homeostatic synaptic plasticity that we will discuss does exactly that: the neuron’s total responsiveness is scaled up or down, while each synapse maintains its relative “weight.” Therefore, this type of homeostatic plasticity was termed synaptic scaling [7].

The first demonstrations of synaptic scaling come from experiments in vitro, where one neuron was recorded and the surrounding network activity was manipulated [7, 8]. The researchers found that blocking inhibitory signaling, which enhances the network activity, made the recorded neuron less responsive. Also, a decrease in AMPA receptors was observed. Conversely, when excitatory network activity was blocked, the neuron showed increased responsiveness and an accumulation of AMPA receptors. Moreover, a change in the composition of the AMPA receptors was demonstrated: more of the subunit GluA1 was inserted, which increased the neuron’s excitability [8].

In 2013, synaptic scaling was demonstrated in vivo: experimenters visually deprived rats on one side (blindfolded one eye) and recorded from neurons that usually received visual input from that eye. These neurons would, after an initial silent period, resume their firing, and re-established the baseline firing rate that was typical for those neurons [9]. This experiment shows that there is compensatory tuning of neuronal activity, dependent on experience.

Since 1998, studies have demonstrated synaptic scaling in response to altered network activity, mostly by measuring changes in AMPA receptors, or the currents that are associated with these receptors: AMPA-R-mediated currents (reviewed in [2, 6]). That is not to say that the AMPA-R always changes in the same way during synaptic scaling. Rather, different circumstances evoke changes in specific receptor subunits, and each subunit has a different effect on the receptor function. For instance, the insertion of the GluA1 subunit makes the AMPA receptor more permeable to Ca^{2+}, which then increases the excitability of the synapse, but other subunits have different effects.

Synaptic scaling is a delicate and fine-tuned system with a high variety of effectors and mechanisms. And to make matters more complicated: while it was first described as a neuron-wide effect, it actually can occur at separate synapses, as we will see next.

Synaptic homeostatic plasticity has been shown to occur selectively at single synapses, given very localized or distinct synaptic input. As an example, consider this study in optic neurons in tadpoles. The optic neurons receive visual input from optic nerves, or pressure (vibration) input from mechanosensory nerves, at different synapses. Using localized electrophysiological recordings, the experimenters could measure the amplitude of the evoked currents in response to input from either synapse. They found that depending on the type of input, different synapses
Recent Advances in Homeostasis

displayed homeostatic changes in current amplitudes [10]. In an experiment with cultured neurons, it was even demonstrated that two adjacent dendritic spines can independently apply postsynaptic homeostatic plasticity: one of the spines received input from a neuron with inhibited activity (due to overexpression of a K^+ channel), and only that spine showed an increase in AMPA-R-mediated current in response—to compensate for this reduced activity [11].

In the previous paragraph we have seen examples of very localized synaptic scaling. Although in some of these processes gene transcription is involved, it is not required for all types of localized homeostatic synaptic plasticity. Within dendritic spines, local protein translation allows for the rapid up- or down-regulation of receptors without the involvement of gene transcription. It is therefore not needed for the neuron to arrange this centrally in the nucleus. However, when synaptic scaling occurs in the whole cell, it usually involves gene transcription, increasing the timescale to days [12].

When it comes to the mechanisms involved in postsynaptic homeostatic plasticity, many intracellular signaling pathways are involved. Similar to LTP and LTD, intracellular calcium signaling plays an important role. In response to synaptic input, Ca^{2+} enters a neuron through a Ca^{2+}-permeable ion channel (either voltage- or ligand-gated) or is released from intracellular stores upon activation of a second messenger. When the intracellular Ca^{2+} levels rise, it serves as a starting point for molecular signaling pathways. The extent of the Ca^{2+} rise is related to the strength of the synaptic input, so Ca^{2+} levels serve as an indicator for the level of activity. How does Ca^{2+} then activate homeostatic processes?

Many different routes and effects have been demonstrated in experiments, that all rely on different signaling pathways and protein kinases, which we have introduced briefly in the introduction. To illustrate (an important) one, consider the example where there is a drop in network activity. This leads to decreased Ca^{2+} signaling in the soma of the postsynaptic neuron. As a result, there is reduced activation of a specific Ca^{2+}-dependent kinase: CaMKIV. Under normal conditions, CaMKIV regulates the transcription of certain AMPA-R subunits. Because of the drop in Ca^{2+} and the subsequently reduced functioning of CaMKIV, the transcription that is normally regulated is now enhanced, which leads to increased production of specific AMPA-R-subunits (in this case: primarily GluA2). Also, it leads to the production of more vesicles that transport these subunits to the postsynaptic membrane [13]. For a simplified visualization of this process, see Figure 3. As you might have guessed, this leads to enhanced AMPA-R-mediated currents, and thus, increased excitability. This is just one example of a Ca^{2+}-mediated mechanism in homeostatic synaptic plasticity in the postsynapse.

Depending on which kinases or signaling pathways are involved, a change in Ca^{2+} levels may trigger different kinds of effects. We have just seen how it can affect the transcription of genes that affect receptor expression and—functioning, but also influences the trafficking (transport) of the receptor (subunits) toward the membrane. But Ca^{2+} signaling can also have effects without involving gene transcription. As we have just discussed, single dendritic spines can also undergo synaptic scaling and for this, only local protein translation is required. In addition to the insertion of AMPA receptor subunits in the postsynapse, this may also have effects on other proteins that indirectly influence receptor function. An example of such local effects involves specialized proteins that are present in the postsynaptic membrane: transmembrane AMPA-receptor Regulating Proteins (TARPs). They are operated by a different calmodulin protein kinase, CaMKII. CaMKII can phosphorylate (and hereby
activate) TARPS, which (as the name suggests) regulate AMPA-R, by connecting AMPA-R to scaffold proteins such as PSD (postsynaptic density)-95. PSD acts as a sort of “anchor” for the AMPA-R; it keeps the receptor inserted. This is an example of stabilizing a receptor, which can increase the functioning of the receptor and thereby, enhance the responsiveness of the neuron. In addition to PSD-95, several other postsynaptic density proteins have been identified to play a role in homeostatic signaling (as reviewed in [14]).

In sum, neurons can counterbalance their excitability by strengthening or weakening synapses postsynaptically, either locally or globally, and this affects mostly the function or expression of (AMPA) receptors. But as we will see in the next section, homeostatic plasticity is not restricted to the postsynapse.
2.2.2 Presynaptic regulation of neurotransmitter release

Synaptic signaling does not only rely on receptor functioning in the postsynaptic neuron. The amount of neurotransmitter released by the presynaptic neuron is of course also a crucial determinant of neuronal activity. As we will see in this section, homeostatic synaptic plasticity can also occur presynaptically, by influencing the release of neurotransmitter (exocytosis).

Most of the work on presynaptic homeostatic synaptic plasticity was done in Drosophila (fruit flies), in the neuromuscular junction, which is where a neuron innervates a muscle cell. Here, it was first shown that when there was less activity in a muscle cell, the neuron that innervated this muscle cell excreted more neurotransmitters [15]. Apparently, a homeostatic mechanism takes place at the presynapse that compensates for reduced activity at the postsynapse. This implies that the presynaptic neuron has to receive a feedback signal that “informs” the presynaptic cell on the level of activity at the synapse. How does this work? First, it has been shown that presynaptic autoreceptors play an important role herein. As the term suggests, presynaptic autoreceptors are receptors that are located on the presynaptic neuron and are activated by the neurotransmitter that is produced by the very same neuron (see Figure 1). Thus, the amount of activated presynaptic autoreceptors is indicative of the activity levels in the synapse. Consequently, the neuron can regulate neurotransmitter release of their own neuro to adjust or restore synaptic activity. Second, it is thought that the feedback signal occurs via retrograde messengers. Retrograde messengers are compounds that are released by dendrites (so, postsynaptically) in response to strong input. They travel back (retrograde) through the synapse, where they bind to receptors that, when activated, influence neurotransmitter release (examples of these retrograde messengers and related mechanisms are reviewed in [16]).

Just like postsynaptic mechanisms, homeostatic presynaptic plasticity is also largely dependent on Ca\textsuperscript{2+}. Retrograde messengers and the activation of presynaptic autoreceptors result in changes in Ca\textsuperscript{2+} influx into the presynaptic neuron. As you may remember from the introduction, intracellular Ca\textsuperscript{2+} signaling regulates exocytosis: the fusion of vesicles containing neurotransmitters with the membrane, upon which the neurotransmitter is released into the synapse. Changes in the Ca\textsuperscript{2+} levels are therefore a direct trigger for increased or decreased neurotransmitter release into the synapse, and this does not necessarily involve gene transcription (see [17]). To summarize, the presynaptic regulation of neurotransmitter release provides a rapid mechanism that contributes to homeostatic synaptic plasticity.

2.3 Network-level homeostasis: the role of glia

So far we have discussed homeostatic mechanisms in pre- and postsynaptic neurons. But as you know, neurons are not the only type of cells that make up a neuronal network. The other type is the glial cells, or glia. Glia come in many different subtypes, and serve many functions: they play a role in the brain’s immune response (neuroinflammation), remove cellular waste products, and guide neuronal growth and development. Glia have long been called the “supporting cells,” but that would be an understatement; communication between neurons in the brain could not take place without glia.

Astrocytes are a specific subtype of glia. In addition to their role in neuroinflammation, they maintain the integrity of the blood–brain barrier. In neuronal networks, they form connections with other astrocytes and with neurons. Many synapses are
surrounded by astrocyte processes, which is why the term “tripartite synapse” is sometimes used—this indicates the presence of a presynaptic neuron, a postsynaptic neuron, and an astrocyte. As you may recall from the introduction, astrocytes are known to take up excess ions (primarily K⁺) after neuronal signaling, removing them from the synaptic cleft (see Figure 1). Through this, they have a “buffering” function and help to keep ion distribution in balance. They do the same for neurotransmitters, for example, astrocytes take up excess glutamate and thereby contribute to glutamate homeostasis. These are illustrations of direct glia-mediated homeostatic mechanisms to control neuronal activity. As we will see next, there are also indirect mechanisms through which glia contribute to homeostasis.

During neurodevelopment, glia are responsible for “pruning”: removal of synapses that are redundant. Through pruning, glia help to establish a stable neuronal network, where there is a balance between excitation and inhibition. When redundant synapses are not pruned, it can lead to excessive connectivity which disrupts this balance. As such, glia are critical in creating a healthy neuronal network where activity remains within functional limits.

As stated before, glia are also the mediators of neuroinflammation. Glia produce cytokines, which are signaling compounds that play a role in inflammatory reactions. Interestingly, many cytokines are also involved in neuronal signaling. For example, consider tumor necrosis factor—alpha (TNF-α), a compound with many functions in the central nervous system (see for a review). TNF-α is produced by neurons, but also (and primarily) by glia. An increase in TNF-α can trigger enhanced glutamate release and also AMPA receptor expression [18]. This too is an example of the indirect effects of glia on neuronal activity.

The examples mentioned here suggest that there is a link between neuroinflammation and the excitability of neuronal networks. In inflammatory conditions, for example caused by an infection or damage to the neural tissue, glia become reactive. This serves to battle the infection or damage, but it has a downside: reactive glia show compromised homeostatic functioning, which can have consequences for brain function, as we will discover in the next section.

2.4 Disrupted homeostasis in brain disease

If homeostasis is disrupted, neurons cannot keep their excitability within limits. As you can imagine, this will have detrimental effects on brain function. In this section, we will briefly highlight two examples of brain diseases where disturbed homeostasis is known to be involved. Bear in mind that disrupted homeostasis may actually play an important role in numerous other brain diseases—what we describe here is just the tip of the iceberg.

The first brain disease with a clear link to disrupted homeostasis is epilepsy. Epilepsy is a neurological disorder affecting millions of patients worldwide. As you probably know, the main symptom of epilepsy is epileptic seizures. During a seizure, there is abnormal, excessive, and uncontrolled firing of neurons. In epileptic brains, neuronal networks tend to be hyperexcitable—the homeostatic control of neuronal activity is apparently not functioning as it should. The challenge in epilepsy research is to find which processes cause this malfunction of homeostasis. Increased neuroinflammation is suspected to play an important role here (although many other factors are thought to contribute as well—see for a review [19]). To illustrate the link between neuroinflammation and increased excitability, consider the role of astrocytes. In response to damage or infection (or other inflammatory circumstances), astrocytes
Recent Advances in Homeostasis

going activated: they become “reactive” to respond to the damage or infection, as was already mentioned in the previous section. When astrocytes become reactive, their glutamate and K⁺ buffering capacities decrease. To illustrate this, an experiment showed that there is decreased expression of the Excitatory Amino Acid Transporters 1 and 2 (EAAT-1 and EAAT-2) in epilepsy patients. EAAT-1 and EAAT-2 are glutamate transporters that are normally found on glia—they mediate the glutamate buffering function of astrocytes. In this research, it was also shown that decreased EAAT expression coincides with astrocytes being reactive [20]. When glutamate is not sufficiently taken up by astrocytes, it is available in synapses much longer—which can lead to more AMPA-R-mediated signaling and thus, enhanced excitatory neuronal activity. Of note, reactive astrocytes are not only seen in epilepsy, but also in other brain diseases.

Disrupted homeostasis is thought to contribute to the pathology in several psychiatric illnesses as well. For example, the malfunction of presynaptic dopaminergic autoreceptors has been shown to play a role in schizophrenia and ADHD. To briefly explain this: the autoreceptors on dopaminergic cells normally inhibit the release of dopamine when they are activated—they are key in the feedback loop that keeps dopamine signaling within limits (review section 2.2.2 for a description of presynaptic autoreceptors). In mouse models and in human patients, it has been shown that this feedback mechanism is not functioning properly, which leads to excessive dopamine release [21]. Excessive dopamine signaling is known to underlie schizophrenia, but may also play a role in ADHD.

These are only a couple of examples showing the possible consequences of disrupted homeostatic control of neuronal activity, and they clearly illustrate the importance of homeostasis in the brain. Restoring homeostasis may be (at least a big part of) the solution for many diseases but is extremely difficult to achieve.

There is no treatment that selectively tunes one process to reinforce homeostasis in a specific neuronal network, nor is there a “reset-button” to restore homeostasis once it has been disrupted. Throughout this chapter, we have briefly and globally addressed some of the mechanisms that control neuronal activity. These (and other, non-discussed) mechanisms all work simultaneously to produce and maintain homeostasis, and often, interfering with one also has consequences for another. As you may have gathered from this chapter, homeostasis is a very intricate and sensitive set of mechanisms that is crucial for healthy brain functioning.

3. Discussion

The human brain contains billions of neurons. Every neuron communicates with thousands of other neurons, so there are trillions of connections within the brain. The connections within and between neuronal networks are formed and shaped by neuronal activity, which means that neuronal activity is subject to, but also causes, a high degree of plasticity. This plasticity is critical for learning, but it also poses a challenge: neuronal activity needs to be limited to remain functional. Excessive neuronal firing hampers information transfer and could lead to epileptic seizures. On the other hand, if neurons are not active at all, you would not be able to think, feel, or act. Homeostatic mechanisms ensure that neuronal activity remains within a functional range. In this chapter, we have discussed the basics of homeostatic control of neuronal activity.

Homeostatic control of neuronal activity aims to restore neuronal excitability to baseline. Interestingly, homeostatic mechanisms also depend on plasticity in the
brain. We distinguish two types of homeostatic plasticity: homeostatic intrinsic plasticity and homeostatic synaptic plasticity. In homeostatic intrinsic plasticity, neurons tune their own intrinsic firing properties, for example by adjusting voltage-gated ion channels, as we have seen in section 2.1.

Homeostatic synaptic plasticity targets neurotransmitter-dependent signaling. In section 2.2.1, we discussed synaptic scaling: a neuron strengthens or weakens its connections by adapting its receptor expression or adapting the receptor subunit composition. In addition to postsynaptic mechanisms, homeostatic synaptic plasticity can also be presynaptic, such as the control of neurotransmitter release by the activation of presynaptic autoreceptors, discussed in section 2.2.2.

In section 2.3, we have discussed the role of the glia in the homeostatic control of neuronal activity, from which we can understand the link between neuroinflammation and disrupted homeostasis. Disrupted homeostasis contributes to brain diseases such as epilepsy, or psychiatric illnesses, as we have seen in section 2.4.

An interesting proposition is that these (and other) brain disorders can arise because of the high degree of plasticity in neuronal networks. In other words, maybe there is a price we pay for our adaptive brains.

If brain disorders are the other side of the coin of neuronal plasticity, where does that leave homeostatic plasticity? As we have seen throughout this chapter, the synaptic plasticity that enables learning (LTP and LTD; we call this Hebbian plasticity) shares molecular mechanisms with homeostatic plasticity. It has been proposed that Hebbian and homeostatic plasticity are basically the same process, but with different outcomes: for learning, the plasticity is used to reinforce activity, whereas for homeostasis it is used to compensate activity. If they use the same (or highly similar) molecular mechanisms, it is still unclear how and why neurons can display different forms of plasticity, with different outcomes. Another question then is: why does homeostasis not counteract learning? Future research will undoubtedly address these complicated questions.

In this chapter, we have attempted to give you a basic overview of homeostatic control of neuronal activity. We hope it has inspired you to explore this topic further; there is much more to learn about homeostasis in the brain.

Author details

Cato Drion
University of Groningen, Groningen, The Netherlands

‘Address all correspondence to: c.m.drion@rug.nl

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References


