Neurons encode information in fast changes of the membrane potential, and thus electrical membrane properties are critically important for the integration and processing of synaptic inputs by a neuron. These electrical properties are largely determined by ion channels embedded in the membrane. The distribution of most ion channels in the membrane is not spatially uniform: they undergo activity-driven changes in the range of minutes to days. Even in the range of milliseconds, the composition and topology of ion channels are not static but engage in highly dynamic processes including stochastic or activity-dependent transient association of the pore-forming and auxiliary subunits, lateral diffusion, as well as clustering of different channels. In this review we briefly discuss the potential impact of mobile sodium, calcium and potassium ion channels and the functional significance of this for individual neurons and neuronal networks.

Introduction

Voltage-gated ion channels modulate the electrical properties of the membrane and thereby play a crucial role in the integration and processing of information by neurons. Many studies have shown that proper localization of ion channels along the neuronal membrane is tightly regulated by various mechanisms and is important for normal neural function, as recently reviewed. Interestingly, stochastic opening of voltage-gated ion channels and lateral mobility within the plane of the membrane also influence their function and localization. A growing body of evidence accumulated in recent years shows that the surface membrane dynamics of ion channels is not just a noise but constructive variable. In particular, the development of high-resolution imaging techniques demonstrated that dynamic activity-dependent redistribution of ionotropic receptors in the synaptic membrane as a complementary mechanism of short-term synaptic plasticity might also be relevant for voltage-gated ion channels.

Aspects of surface dynamics

Molecular dynamics of ion channels has been related to either the structural dynamics of the pore-forming subunit, allowing the passage of ions through the membrane, or to lateral diffusion in the cellular membrane caused by its sub-cellular heterogeneity. The need of molecular motions for the opening and closing of ion channels is well defined and is in the range of a few Angstroms (or several hundred picometers). However, the functional impact of diffusive voltage-gated ion channels, which can explore hundreds of nanometers on the cell surface, varies between different channels and involves multiple mechanisms. The membrane viscosity and thermal energy stored in the plasma membrane are necessary for the flexibility of molecular machinery to be functional as we know it, e.g., from the orchestrated action of ion channels during an action potential (AP). Ion channels are multimeric complexes with a central pore-forming subunit that is often bound to other subunits with different affinities. Hence, lipids that agitate membrane proteins by their stochastic motion will introduce an alteration in the lateral dynamics of channel complexes that may alter molecular interactions. Using single particle tracking, one can describe distinct modes of diffusive motion based on analysis of localization (trajectories) of particles over time. The existence of diffusion barriers in the neuronal membrane, such as between the somato-dendritic compartment and the...
axon, underlines the importance of surface diffusion in imposing rapid changes to ion channel organization. Furthermore, a strict diffusion barrier between the somatodendritic compartment and the axon, called axon initial segment (AIS) is important for the maintenance of the polarity of a neuron and thereby contributes to the directed transfer of information in neuronal networks. Tight control of ion channel density and composition in the AIS is key in the regulation of neuronal excitability, and disturbance of the scaffold organization within the AIS immediately leads to a diffusion-driven decrease in ion channel density and thus corresponding changes in the excitability of the neuron. Apart from this neuron-specific structure, most of the surface expressed voltage-gated ion channels are mobile within cellular membranes. The existence of such surface mobility produces the potential to characterize molecular interactions of the observed molecule based merely on changes in its diffusion behavior. Given that kinetic properties of most ion channels depend not only on the pore-forming subunit, but to a large extent on the assembly and interaction with accessory subunits, one can assume that channel composition, and hence function, might be tuned by a dynamic assembly over time. A striking example for such local transient interaction has been shown for calcium channels in cardiac myocytes, where clustered organization of Cav1.2 determines the size of the intracellular calcium domain and is essential for the excitation-contraction coupling. As demonstrated by Dixon et al. (2015), transient interactions of Cav1.2 channels with each other via the C-terminus, which lead to positive cooperativity at opening, depends on, but persists longer than, the initial calcium influx and may reflect a kind of “molecular memory” imprinted in the local organization of calcium channels. Thus, the dynamic organization of ion channel clusters along the neuronal membrane might indeed serve as a readout for such molecular memory traces that carry the potential to trigger long-lasting changes in neuronal excitability.

**Mobility in the crowded environment of the membrane**

Embedded into the plasma membrane, ion channels are part of a viscous membrane structure built up from oriented lipids and integrated proteins. The multimeric complex around the pore-forming subunit of an ion channel, as well as the position of the pore-forming subunit itself, might be defined by stochastic motion in small compartments. In early experiments, visualization of the dynamics of biological membranes using fluorescence recovery after photo bleaching (FRAP) provided evidence for the fluid-mosaic model of membrane organization. The use of single particle tracking (SPT) led to a more detailed analysis of molecular mobility in the plasma membrane, mainly by opening access to the diffusion properties of individual molecules over time. The membrane-attached cytoskeleton and extracellular structures, as well as the structural heterogeneity of the membrane, produce a mosaic-like pattern of the membrane, with individual molecules being able to escape distinct areas by so called hop-diffusion. Hence, the mobility of the molecules brings dynamics to the molecular composition of membrane mosaics and allows for the exchange of molecules, modulated by their interactions with other membrane molecules, intracellular partners and/or extracellular structures. This can be important, since channel-independent functions of auxiliary subunits have been proposed in several studies.

Thus, with the development of super-resolution microscopy techniques and the availability of genetic tools to attach fluorescent labels to ion channel proteins, it is now possible to visualize channel location during repetitive opening and closing and to address the question whether channels are dynamic in the cellular membrane, the contribution of molecular interactions and the impact of ion channel dynamics to cellular excitability and synaptic communication. Below, we summarize the data on surface dynamics for sodium, calcium and potassium channels and its proposed functional impact.

**Na\textsubscript{v} channels**

Voltage-gated sodium (Na\textsubscript{v}) channels mediate inward sodium currents and play a crucial role in the generation and propagation of APs. Functional sodium channels consist of a pore-forming \(\alpha\) subunit (Na\textsubscript{v}1.1-Na\textsubscript{v}1.9) associated with one or more auxiliary \(\beta\) subunits (\(\beta1-\beta4\)). Although, the \(\alpha\) subunit is sufficient for expression of functional channels, auxiliary \(\beta\) subunits modulate the gating, voltage-dependence and kinetics of the channel, as well as its localization and interaction with intra- and extracellular scaffolds. In central neurons, Na\textsubscript{v}1.1-1.3 and Na\textsubscript{v}1.6 are the primary sodium channel isoforms, while
Nav1.7-1.9 are expressed predominantly in peripheral neurons. Additionally, sodium channels are expressed in non-excitable cells where they can serve non-canonical functions. Consistent with their role in generation and propagation of action potentials, sodium channels cluster at high density in the AIS and nodes of Ranvier. However, some Nav isoforms are also expressed in somato-dendritic compartment and synaptic locations. The local surface distribution/dynamics of sodium channels in the membrane has not been studied extensively, but in an early study their mobility was found to be at least one order of magnitude slower in the AIS in comparison to somatic membranes. This can be related to direct binding of NaV channels with Ankyrin G that serves as a master scaffold protein and forms the AIS structure for other proteins. NaV1.2 and NaV1.6 were recently shown, using SPT, to undergo Ankyrin G-dependent confinement in the axonal membrane, while channels in somatic membrane often remained mobile. Recently, the AIS has been shown to be not only a platform to lock channels in high density, but to be a dynamic structure that tunes neuronal excitability. Depending on the spacing between cell body and the proximal end of the AIS, as well as the total length of the AIS, neurons can shift their action potential threshold up and down within a couple of hours. The density and kinetic properties of NaV channels and voltage-gated potassium channels (Kv) contribute to the fine-tuning of the action potential threshold as a response to changes in network activity. Whereas chronic bursting activity moves the AIS away from the soma, a loss of sensory input leads to an enlargement of the AIS, resulting in a higher or lower threshold for the initiation of an action potential, respectively. The tuning of the action potential threshold is critically dependent on the activity of voltage-gated calcium channels and the density and kinetic properties of NaV and Kv channels. Crucial questions, such as how channels are inserted into and removed from membranes and whether there are density gradients in Na, and K, channel expression along the AIS, can now be answered with the observation of channel dynamics in the membrane. Interestingly, both ion channel populations (NaV and Kv) are linked to the Ankyrin G scaffold via similar binding motifs. In NaV1.1, NaV1.2, NaV1.3 and NaV1.6 this motif is located in the α-subunit within the intracellular linker between segment II and III. A similar binding motif is found in the distal part of the C-terminus of KCNQ2/3 (Kv7.2/Kv7.3). Though NaV channels and Kv7.2/Kv7.3 channels share an overlapping binding domain on Ankyrin G, the affinity of sodium channels for Ankyrin G is much stronger. The binding of both channel populations to Ankyrin G is modulated by casein kinase 2 (CK2) phosphorylation. Blocking CK2 activity leads to a dephosphorylation of the binding motif and greater surface dynamics of NaV channels. Alterations to ion channel composition and AIS size are known mechanisms of neuronal excitability tuning. It remains to be explored whether the surface dynamics of NaV and Kv channels contribute to such alterations in AIS size or position.

Another speculative function of membrane dynamics is the variability of NaV channel composition. Auxiliary β-subunits are known to alter channel conductance and kinetics, subcellular localization of sodium channels and they also possess channel-independent functions as adhesion molecules. It is tempting to speculate that the adhesive function of the β-subunits contributes to the confinement of sodium channels in subcellular membrane compartments and can be influenced by the proteolytic cleavage by extracellular proteases, such as the β-site amyloidal precursor protein-cleaving enzyme (BACE1). NaV channels are involved in a variety of profound neurological disorders, including epilepsy, ataxia or augmented pain sensitivity. Understanding the dynamic organization of their membrane localization and subunit composition will help to identify the computational power of sodium channels as key molecules in electrical signaling.

Voltage-gated calcium channels

Voltage-gated calcium channels (VGCCs) are the main source for intracellular calcium changes and convert alterations in membrane potential into intracellular signalling events in excitable cells. The most prominent physiological functions for local calcium channel action are the triggering of vesicular release, triggering of excitation-transcription coupling in neurons, and excitation-contraction coupling in heart and skeletal muscles. Therefore, VGCC activation-driven fluctuations in intracellular calcium concentrations have been the subject of intense investigations.
composed of a pore-forming α1 subunit, an intracellular β subunit and extracellular α2δ subunits. While the role of γ subunits in a functional VGCC is not entirely clear, it is thought that they act mainly as auxiliary subunits of AMPA receptors. The composition and dynamic nature of the channel complex is a major source for functional variability of VGCC (for recent review see 24). Here, the diversity in the expression profile of auxiliary β and α2δ-subunit isoforms in neurons produces a large number of possible combinations with α1-subunits and hence major potential for altering calcium channel activity. The combinatorial capacity depends on the expression profile of different β and α2δ-subunit isoforms and alternative splicing within the cell, which can be variable between brain regions. In respect to the dynamic composition of functional VGCC on the cellular surface, α2δ-subunits are of potential interest. These subunits boost the surface expression of VGCC, stabilize VGCC in the membrane, modulate kinetic properties of α1-subunits, and are potential interaction partners for extracellular matrix proteins and signaling proteins. The α2δ-subunits are associated with the cell membrane via a GPI anchor, whereas the side of α1-subunit interaction is still under discussion. Based on biochemical and structural data, the von Willebrand A (VWA) domain and the Cache1 and Cache2 domain within the α2-subunit interact with the extracellular loops of segment I-III of the α1-subunit. It is also reported that an N-terminal R-domain is sufficient for α1-subunit interaction. Mutation of the VWA domain, particular the metal ion–dependent adhesion site (MIDAS) motif impairs the interaction of the α1- and the α2δ1-subunit and leads to a reduction in current density caused by reduced surface expression of channels as well as mutated α2δ1-subunits themselves, indicating impaired trafficking to the surface. The assembly and affinity between α1-subunits and α2δ-subunits on the cell surface is not well understood. Cleavage of the GPI-anchor by phosphatidylinositol phospholipase C (PI-PLC) results in a release of α2-subunits into the extracellular space and a reduction of CaV2.2 mediated calcium currents. Expression of α2δ1 without membrane anchor leads to a partial increase in CaV2.2-mediated calcium currents and only a partial rescue of the time constant for current inactivation compared to the expression of the complete α2δ1-subunit. These data indicate: the association of α1-subunits and α2δ-subunits is critical for the surface expression of the channels; an alteration of the binding affinity of α2δ-subunits to the α1-subunit destabilizes the surface population of calcium channels and leads to increased endocytosis; the glycosylation pattern is critical for the strength of subunit association and; the stoichiometry between α1- and α2δ-subunits might be in a dynamic equilibrium between channel-bound and channel-unbound α2δ-subunits, since a certain population of α2δ-subunits can be liberated by the cleavage of the GPI anchor. The last aspect is supported by the channel independent function of α2δ-subunits in synaptogenesis and as a binding partner for extracellular matrix molecules. It is tempting to speculate that the dynamic association between α1- and α2δ-subunits is indeed a mechanism to modulate VGCC stability and the kinetic properties on the cell surface. However, so far the natural stoichiometry and dynamic nature of channel subunits in the cell membrane remain to be investigated in more detail since most reports have used heterologous expression systems or transient overexpression of channel subunits in variable combinations, which might bias the ratio between surface expressed channel subunits. By using transgenic animals and expression of tagged α2δ-subunits under the endogenous promotor in muscle cells of the worm C. elegans, it has been reported that a certain fraction of α2δ-subunits is mobile but confined in the muscle membrane (Zhang et al. 2014).

Apart from the auxiliary subunits, which represent the minimal assembly of a functional VGCC, high resolution proteomic approaches have identified many more potential interacting partners and propose that VGCCs are part of macromolecular complexes. Within chemical synapses, the communication compartment between neurons and local interaction partners has a strong impact on channel kinetics and signaling capacity of VGCC. Particularly for CaV2 channels, which include P/Q-, N- and R- types, a large number of interacting molecules have been identified. Here, local calcium changes play a critical role both in neurotransmitter release at the presynaptic active zone and in the induction of long-term
changes at the postsynaptic density. Along dendrites, VGCCs are involved in sensing neuronal activity changes, as well as, by triggering different signaling pathways, modulation of gene expression and maintenance of cellular homeostasis. Given these important functions of VGCC in intracellular and intercellular signaling, the positioning of VGCC in respect to calcium-sensitive intracellular molecules is of high relevance for the signaling capacity of calcium fluxes. In most models, the positioning of calcium channels has been assumed to be fixed in place to maximize the signaling capacity of local intracellular calcium domains of opened channels without crosstalk to neighboring entry sites, but there is an accumulating body of evidence to suggest otherwise. In addition, the fast action of intracellular calcium buffers and calcium-binding proteins support this picture. Changes in the conductivity, steady-state inactivation by the interaction with SNARE proteins such as syntaxin and SNAP 25, as well as calmodulin mediated calcium-dependent inactivation/facilitation are considered as the self-possessed properties of the channel that determine its signaling capacity. As proposed by Tadross et al., the induced calcium domain of one VGCC (CaV1.3) seems to be restricted to a few nanometres – but with a much higher amplitude than assumed before. Hence, the signaling capacity of VGCCs seems to be maximised by their local action and implies a signaling precision within a membrane domain of < 100 nm. Given that the positioning of each calcium channel seems to be relevant to achieve the full signaling capacity, single channel-induced intracellular calcium changes have been explored. However, the use of the intracellular calcium transients induced by the opening of one, or small clusters of VGCC called sparklet, as readout for channel localization over time is difficult, since the kinetic of intracellular calcium signals and dynamics of membrane proteins are very different. Direct measurement of calcium channel surface dynamics in the cell membrane has been made possible by well-defined fluorescent probes attached directly to the pore-forming subunit or associated α2δ-subunits. Calcium channel dynamics differs along the neuronal membrane, but the majority of channels are confined in clusters along the membrane, as described for CaV1.2. In the axonal membrane, CaV2.1 and CaV2.2 channels are mobile, but confined in presynaptic-terminals. Therefore, the contribution of channel mobility to calcium-mediated signaling is most likely a local variable within zones of confinement along dendrites and axons, which are a few hundred nanometres in diameter. Within such membrane areas (illustrated in Fig. 1), as the presynaptic active zone or postsynaptic spines, small, but dynamic, populations of VGCCs can substantially improve the capacity of the calcium signal as suggested for the presynaptic vesicle release probability. In the presynaptic active zone, the relatively low calcium sensitivity of the vesicular calcium sensor proteins demands a very close alignment of calcium channels and releasable vesicles within a radius below 100 nm. Investigations of the release probability, channel distribution, as well as evoked calcium signals, point to a clustered distribution of presynaptic calcium channels. The distance of VGCC clusters and synaptic vesicles varies between different synapses and implies different channel arrangements in the different synapses. Bearing lateral diffusion in mind, several options for modulation of synaptic release probability and short-term plasticity emerge. Here, dynamic arrangement might compensate for the kinetic properties of channels by lateral exchange of inactivated channels, and the individual release probability of vesicles would be more flexible due to the ever-changing position of releasable vesicles and active channels. This idea is supported by the observation that increase of calcium channel numbers in synapses by overexpression of α2δ1 subunits does not lead to a tighter clustering of VGCCs, but causes an enlargement of the active zone without altering channel dynamics and increase presynaptic release probability. In addition, altering intracellular calcium transients of open channels by fast exogenous calcium buffers like BAPTA does not only reduce the dispersal of the intracellular calcium domain but also decreases the radius of channel confinement, supporting the argument that a flexible positioning of calcium channels within a membrane domain does contribute to their signaling capacity in synapses. A further example for nanometre-range molecular interactions, probably vulnerable to surface diffusion
and relevant for neuronal excitability, is the interaction of VGCCs and BKCa channels. BKCa channels have a conductivity of 200-300 pS: 10-50 fold higher than other potassium channels. The opening of a few BKCa channels can induce a substantial outward potassium current and thus even on the single channel level are of physiological relevance. Their activation depends on the tight association with VGCCs, calculated to be in a critical radius between 10-15 nm. A dynamic association between BKCa channels and VGCC could be a very fast mechanism to regulate BKCa channel activity. As predicted by a modeling approach, activation of BKCa channels could be dramatically altered by very small displacements of 10-50 nm. Despite the numerous binding partners identified for BKCa channels and VGCC, the reported diffusion coefficients for both channels are in the range of 0.005-0.05 μm²/s and could facilitate diffusion-driven displacements of BKCa channels and VGCC for 10-30 nm within a physiologically relevant time interval of 10 ms. It should be noted however, that the ideas discussed here presume that action of individual VGCCs are independent from each other, as reported for the presynaptic-terminal of GABAergic neurons. However, the above mentioned data obtained in cardiomyocytes showed that calcium-dependent binding of calmodulin to the C-terminal IQ-domain of neighboring channels induces...
positive cooperativity of $\text{Ca}_V$1.2 channels. They whether dynamic binding and unbinding from identified scaffold protein can induce similar cooperativity, for instance in the active zone of the presynaptic membrane or complexes with BK$_{\text{Ca}}$ channels, requires further investigation.

**Potassium channels**

Voltage-gated potassium channels ($K_v$) control electrical excitability in skeletal muscles, cardiovascular system and the nervous system. They play a key role in establishing the resting membrane potential, shaping AP repolarization phase, and in influencing the amplitude, duration and frequency of APs. Therefore, changes in the number and location of surface potassium channels can profoundly affect electrical excitability and neuronal plasticity. Potassium channels comprise the largest, and at the molecular level the most diverse, class of ion channels, which contains over 80 genes encoding for the channel's principal (or $\alpha 1$) subunits. $K_v$ channels exist as multi-subunit complexes formed by typically 4 $\alpha 1$ subunits (2 in case of 2-pore $K_v$) and variable number of associated auxiliary subunits. These auxiliary subunits are not essential for ion permeation, but regulate channel trafficking and gating, and may be necessary for modulation of the channels by protein kinases or other signaling pathways. Potassium channels are found in virtually every neuronal compartment, including dendrites, axons, cell bodies and presynaptic-terminals, nodes of Ranvier, AIS and dendritic spines. In respect to the topic of the review, local diffusion-driven reorganization of some $K_v$ channels has been reported. For example, $K_v$ channels can interact with $\text{Ca}_V$ channels via intracellular auxiliary subunits. The $K_v$ channel interacting proteins (KChiPs) are $\text{Ca}^{2+}$-binding proteins that interact specifically with $K_v$ channels and regulate voltage dependence of inactivation. In cerebellar neurons, KChiPs exist in complexes with $K_v$4.2 and T-type ($\text{Ca}_V$3) calcium channels, thus the position of VGCC and $K_v$ channels in macromolecular complexes seem to be essential for channel function and can be dynamically organized.

Calcium-activated potassium channels open by the cooperativity of 2 stimuli, voltage and intracellular calcium. Depending on their association with auxiliary $\beta$- and $\gamma$-subunits, the voltage and calcium dependence of BK$_{\text{Ca}}$-channels are drastically changed. The coupling distances between BK$_{\text{Ca}}$ channels and VGCC have been estimated to be in the range of 10-20 nm, whereas SK$_{\text{Ca}}$ channels with higher calcium sensitivity are also activated if they are more than 100 nm away from the VGCC. The impact of dynamically organized BK$_{\text{Ca}}$ channels and VGCCs has been discussed above. A dynamic distribution of SK channels has been not explored yet. Given that VGCC or NMDA receptors are mobile but confined in small clusters along the dendritic membrane, one can assume that the availability of SK channels within the critical distance of 100-200 nm from VGCC might be achieved by lateral dynamics in subcellular compartments like synaptic spines. Interestingly, depending on subcellular localization, BK$_{\text{Ca}}$ channels exhibit heterogeneous lateral mobility in the plasma membrane. Channels located in the neuronal cell bodies are rather static, whereas those in dendritic areas are highly mobile. Intriguingly, this lateral movement is dramatically changed when the auxiliary $K_v$$\beta$ subunit is co-assembled with a channel: the channel's mobility is decreased in axo-dendritic areas, while the channels in the soma become much more mobile after $K_v$$\beta 4$ subunit co-expression. This indicates that in the same subcellular compartment, BK$_{\text{Ca}}$-channels may have different composition and conductance, as well as different surface dynamics that result in altered coupling frequency to VGCC and distinct functional consequences. The impact of $\gamma$-subunits on channel confinement has not been explored. Based on the leucin rich repeat of the extracellular domain, one can speculate that not only kinetic properties are dramatically changed, but also localization.

Another interesting feature of potassium channel mobility has been reported for the delayed rectifier potassium ($K_v2.1$) channels, which predominantly mediate the delayed rectifier current in neurons. The expression of $K_v2.1$ channels is restricted to the soma and proximal dendrites in hippocampal and cortical neurons *in vitro* and *in vivo*, where $K_v2.1$ channels form unique cell surface clusters. The actin cytoskeleton is required to keep channels within a cluster, because actin depolymerization results in channel declustering. The cluster formation is also related to phosphorylation of $K_v2.1$ and membrane depolarization, and subsequent calcineurin activation causes $K_v2.1$ declustering. In parallel, channel...
dephosphorylation leads to a hyperpolarized shift of the channel activation.97,98 Such fragmentation of the clusters and shifts in voltage dependence of activation occurs in cultured neurons in response to various excitatory stimuli, e.g. chemically induced ischemia, glutamate and elevated Ca2+.97 FRAP experiments suggest that Kv2.1 containing clusters represent stable and well-defined regions at the cell surface. Exocytosis of Kv2.1 channels to the plasma membrane appears at first to be diffuse, but remains constrained to the point of delivery.108 In addition, labeling of individual Kv2.1 channels with quantum dots demonstrated that they are mobile within confined membrane domains and remain clustered at the membrane.59 Within these domains, channels collide with each other and sometimes escape the domain.108 Cell-attached patch clamp recordings from macro patches of Kv2.1 clusters showed that channels retained within these surface clusters are non-conducting channels and do not contribute significantly to the macroscopic delayed rectifier K+ current.107 However, these “silent” channels sense the membrane potential, as shown by measuring of gating currents that are produced by charge movement of the voltage sensing S4 domain of a1 subunit upon the change of membrane potential. On the other hand, measurements of channel activity under similar conditions from patches of nonclustered Kv2.1 channels revealed robust currents with slow activation kinetics. This suggests that clusters of Kv2.1 channels are trapped in cytoskeletal coral130 and might act as surface reservoirs of non-conducting channels that can be activated by altering local restraints.

The ether-a-go-go (Eag1) or Kv10.1 potassium channels are widely expressed in the mammalian and rodent adult brain,94 but their physiological function is not fully understood. The Eag1 channels are localized primarily in axons, with about 25% being present in the membrane of presynaptic-terminals.59 Endogenous Kv10.1 channels enter and leave synapses by lateral diffusion within the plasma membrane59 and therefore might quickly influence synaptic transmission. These channels exhibit slower mobility inside presynaptic-terminal than outside, and trajectories of synaptic channels are more spatially confined than those of extrasynaptic ones, suggesting restricted mobility in synapses.59 Outside synaptic-terminals, Eag1 channels display free Brownian diffusion. The mobility of Eag1 channels can be regulated by cytoskeleton, since disruption of cytoskeletal network decreases the number of Eag1 channels in synaptic region and increases the number of transitions between synaptic and extrasynaptic locations.59 This suggests that the lateral movement of the Eag1 might be of physiological relevance for neuronal excitability.

In this review, we briefly described the data available on surface mobility of voltage-gated sodium, calcium and potassium channels in the neuronal membrane, however much of the dynamic surface organization of ion channels remains to be explored. Due to fundamental role of ion channels in setting and/or modulating the excitability of the neuronal membrane, they have a direct impact on individual neuronal properties, as well as on the network function.21 The availability of novel molecular tools, such as knock-in mouse models with fluorescently tagged ion channels,51,92 enables us to evaluate several aspects of surface dynamics of ion channels. First, visualization of endogenous channels allows us to visualize the organization of ion channels in their unbiased natural environment, and thereby to overcome disadvantages of over-expression, which often leads to profound alteration of the excitability and homeostatic plasticity of excitable cells.21 Furthermore, these tools provide accessibility to single molecule resolution. Super resolution microscopy approaches with temporal resolution >30 Hz, such as sptPALM, UPaint or SPT,55,80,90 will help to determine the temporal molecular dynamics and organization of ion channel complexes and even enable us to observe those proteins during channel activity. Keeping in mind the astonishing number of potential interaction candidates, as exemplified for AMPA receptors, VGCCs and potassium channels,56,85,89,100,120,121 the combination of single molecular imaging approaches, in conjunction with functional readouts, will facilitate the investigation of multiple facets of the dynamic contribution of ion channels, as both ion conductors and signaling complexes, for the plasticity, formation and maintenance of neuronal connectivity, and will open new vistas for the identification of pathological mechanisms of neurological disorders on the molecular level.

**Abbreviations**

AP action potential
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolopyridinonic acid
BKca large conductance potassium channel
Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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