Chapter

# Electrophysiological Investigations of Prion Protein Roles in Health and Disease

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## Abstract

Prion diseases are transmissible and fatal neurological disorders associated with the misfolding of cellular prion protein (PrPC) into disease-causing isoforms (PrPD) in the central nervous system. The diseases have three etiologies; acquired through exposure to the infectious PrPD, sporadic, arising from no known cause, and hereditary due to familial mutations within the *PRNP* gene. The manifestation of clinical signs is associated with the disruption of neuronal activity and subsequent degeneration of neurons. To generate insight into the mechanisms by which neuronal activity becomes disrupted in prion diseases, electrophysiological techniques have been applied to closely study the electrical signaling properties of neurons that lack functional PrPC as well as neurons that are developing pathological features of prion diseases due to infection or genetic mutation. In this review, we will compile the electrophysiological evidences of neurophysiological roles of PrPC, how those roles are changed in neurons that are developing prion diseases, and how disease-associated effects are exacerbated during the clinical stage of disease.

**Keywords:** prion, CJD, LTP, electrophysiology, PrPC roles

## 1. Introduction

Prion diseases are transmissible neurological disorders that are always fatal following symptom onset. These diseases affect humans and animals. The most common forms in humans are Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), and familial fatal insomnia (FFI). The primary causative event is the misfolding of PrPC into PrPD in the central nervous system, which is followed by progressive impairments of cognition and behaviour. The fundamental roots of the clinical manifestations are the impairments of neuronal activity. In patients, these changes are mostly detected by electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) [1]. The abnormal neuronal activities associated with prion diseases have been successfully modeled in the laboratory using mouse models, cultured mouse primary neurons, and cultured human/mouse induced pluripotent stem cells [2, 3]. As a result of advancements in experimental neuro-electrophysiology technologies, our understanding of neuro-electrical signaling dysfunctions associated with prion diseases has substantially improved over the last decades.

In experimental models, there have been several neuro-electrophysiological phenomena identified in the glutamatergic neuronal system that closely correlate with the underlying molecular mechanisms of memory formation/loss and behavioral change. These include the short-term plasticity (STP), long-term potentiation (LTP), and long-term depression (LTD) [4]. STP is usually detected as a rapid physiological alteration of neuronal activity that lasts milliseconds to seconds immediately after neurons receiving a stimulation [5, 6]. This short-term function is usually due to a rapid enhanced release of neurotransmitters that overwhelmingly activate the preexisting receptors on the post-synaptic terminals [5, 6]. Through such a mechanism, STP can be evoked by a paired-stimulus delivered a few milliseconds apart, in which the post-synaptic response evoked by the second stimulus indicates the probability of neurotransmitter release at a synapse or a population of synapses [5, 6]. Further, with repetitive short (~0.5–1 min) trains of high frequency (~100–200 Hz) stimulation, neurotransmitters are released at a substantial level, which extensively depolarizes the post-synaptic membrane causing activation of the NMDA receptor (NMDAR), a glutamate receptor that modulates the post-synaptic currents when it is active [7]. The post-synaptic response within seconds of the high frequency stimulation is largely STP, reflecting the levels of neurotransmitters release [8]. Repetitive stimuli can also evoke a short-term phenomenon called the afterhyperpolarization, which usually lasts 1 second. Afterhyperpolarization is divided into three parts, the fast (first few milliseconds), medium (100–500 milliseconds), and slow (longer than 500 milliseconds) afterhyperpolarization [9]. The afterhyperpolarization is largely dependent on the activity of potassium channels, especially the calcium-sensitive potassium channels, as well as the activity of voltage-gated calcium channels and the level of intracellular calcium [9, 10].

The activation of NMDARs following a repetitive high frequency stimulation causes externalization of more AMPA receptors (AMPARs). AMPARs are a type of glutamate receptor known as the workhorse of glutamatergic neurons because they can rapidly generate synaptic signaling [7]. The rapid recruitment of AMPARs can subsequently activate neighboring silent synapses, causing excitatory neurons to remain persistently active for hours, a phenomenon called LTP [11]. On the other hand, repetitive and prolonged (~5–10 min) trains of low frequency (~0.5–5 Hz) stimulation cause depolarization of post-synaptic membrane and activation of NMDARs in a way that triggers internalization of AMPARs, causing depression of the post-synaptic current that can persist for hours, a neuro-phenomenon called LTD [4]. While these are the main known mechanisms of LTP and LTD, the fast-growing interest on how these phenomena are induced and maintained has led to the discovery of a wide variety of potential molecular mechanisms.

To understand the mechanisms underlying the neuronal dysfunctions associated with the clinical phenotypes of prion diseases, studies have focused on identifying how the neuro-electrophysiological correlates of cognition and behaviour become impaired in experimental models of disease. In this review, we will discuss the normal neuro-electrophysiological roles of PrPC and the neuro-physiological alterations during the asymptomatic stage to the early onset of clinical signs in models of acquired and genetic prion diseases.

## 2. Neuro-electrophysiology of PrPC

PrPC is a membrane-tethered glycoprotein, targeted to the outer leaflet of the plasma-membrane by a glycosylphosphadiylinositol (GPI) anchor. The precise functions of PrPC in the central nervous system are largely unknown; however,

| Roles of PrPC in cell functions and signaling | Reference |
|---|---|
| Neurotransmitter release | [13, 18–20] |
| Long-term potentiation | [22–24] |
| Metaplasticity | [27] |
| Calcium-dependent potassium channel function | [20, 22, 30] |
| L-type voltage-gated potassium channel function | [10, 20] |
| NMDA receptor function | [14] |
| Voltage-gated calcium channel function | [36] |
| Calcium homeostasis | [10, 20] |
| GABA receptor function | [14, 22, 30, 38] |
| Maintenance of peripheral nerves myelination | [40] |
| Modulator of various signaling functions including Fyn and mGluR5 dependent regulation of NMDAR activity, and modulation of p38 Mitogen Activated Protein Kinase signaling pathway (refer to the subheading: *PrPC regulates major intracellular signaling pathways*) | [33, 42] |

**Table 1.**
*Summary of the normal physiological roles of PrPC including the studies that reported those roles.*

there is considerable evidence to suggest that PrPC has important roles in neuronal activity [12] (**Table 1**). These putative functions of PrPC have been studied by combinations of electrophysiological recordings, genetic modifications, and pharmacological approaches.

### 2.1 PrPC assists synaptic transmission

PrPC is expressed in both pre- and postsynaptic terminals [13–19], where it plays essential roles in synaptic activity. PrPC interacts with presynaptic vesicles and facilitates release of neurotransmitters [13, 20, 21]. PrPC also regulates presynaptic calcium channels, allowing influx of sufficient calcium into the presynaptic terminal to facilitate the release of neurotransmitters [21, 22]. At the post-synaptic terminals, PrPC interacts with various post-synaptic glutamate receptors and regulates their functions (discussed later in this section) [14, 23]. In mice devoid of PrPC expression, it has been found that LTP within the hippocampal CA1 and dentate gyrus is significantly impaired [24–26]. This impairment is associated with memory and behavioral deficits [27]. However, this is still a point of contention as normal LTP within these regions has also been observed and the discrepancy appears un-related to the genetic background of the mouse model [5, 28–30]. Hippocampal CA1 metaplasticity is also impaired in PrP knockout mice; here the post-synaptic responses become enhanced as opposed to being depressed when a low frequency stimulation is paired with a couple trains of theta-burst stimulation (consists of 10 trains delivered at 5 Hz where each train comprises of 4 pulses delivered at 100 Hz) at an interval of ~25 minutes [29]. Further, Juvenile PrP knockout mice exhibit poor sensorimotor performance, which correlates with the cerebellar granule cells displaying slow rate of inward and outward membrane currents, slow kinetics of excitatory post-synaptic responses, and incompetence to induce LTP by theta-bust stimulation [31]. These abnormal phenotypes disappear when the mice reach adulthood [30, 31], thus suggesting that PrPC plays some essential roles in synaptic transmission during early development.

### 2.2 GPI-anchored PrPC regulates ion channels activity

The activity of ion channels is essential for the maintenance of synaptic functions [7]. The involvement of PrPC in ion channel activity has been implicated in mice lacking PrPC [12]. These mice exhibit electrophysiological features of dysfunctional ion channels such as reduced slow and medium afterhyperpolarization in the hippocampal CA1 region, which indicates an impairment of calcium-dependent $K^+$ channels [22, 24, 32]. This finding is consistent with the report that PrPC modulates the activity of voltage-dependent potassium channels [33]. Additionally, the hippocampal CA1 exhibits reduced currents of L-type voltage-gated calcium channels in the absence of PrPC [22], albeit another study showed the contradictory finding [10]. In cultured hippocampal neurons from PrP knockout mice, the activity of NMDARs is significantly impaired. These receptors exhibit a longer decay time and larger amplitude of miniature synaptic currents as well as very slow deactivation kinetics of agonist-mediated currents [14]. The interpretation of these findings was that PrPC functions to prevent hyperactivation of NMDARs.

The contribution of PrPC to ion channel activity has also been reported in a variety of cells expressing PrPC with various primary sequence mutations; designed to determine the effect of each mutant on ion channel activity as a measure of prion neurotoxicity [34]. Several deletions (between residues 94 and 134) in the charged and hydrophobic region of PrP, a conserved region of PrP, cause dysfunction of cation-permeable channels, which increases the inward currents leading to cellular toxicity and cell death [34–36]. The deletion of PrP residues 105–125 or 94–134 causes the most deleterious dysfunction of ion channels. Deletion of other residues such as PrP 94–110, 111–134, and 114–121 also causes similar toxic effect, but at relatively lower degrees [35]. Although these observations have mostly been reported in nonneuronal cells (HEK293T) [34–36], the neonatal death in mice expressing PrP devoid of 105–125 residues affirms that the deleterious effect of this deletion appears independent of cell type [37].

When PrP residues 105–125 are co-deleted with residues 51–90 (a five octapeptide repeat region), the impairment of ion channels becomes slightly reduced [35]. Furthermore, the toxic effect of PrP lacking residues 105–125 vanishes when co-deleted with either the GPI anchor (PrP 231–254) alone or the GPI anchor and the endogenous signal motif (PrP 1–22; to retain PrP in the cytoplasm), suggesting that the toxic PrP needs to be transported out of the cytoplasm and anchored to the lipids in order to disrupt the activity of ion channels. This evidence implies that GPI-anchored PrPC prevents hyperactivity of ion channels. Further support for this role has also been observed using cells lacking GPI-anchored PrP, where the calcium current intensity of voltage-gated calcium channels (containing subunits $Ca_V2.1/\beta$ and $\alpha2\delta$-1 or $\alpha2\delta$-2) becomes reduced in the presence of GPI-anchored PrP but enhanced in the presence of only GPI-anchorless PrP [38]. Taken together, when PrPC is correctly trafficked and anchored to the cell membrane, it regulates the activity of ion channels, predominantly through its charged and hydrophobic region.

### 2.3 PrPC maintains neuronal calcium homeostasis

As aforementioned, PrPC regulates ion channels including the voltage-gated calcium channels and NMDARs. In the absence of endogenous PrPC expression, hippocampal CA1 neurons exhibit dysfunction of calcium homeostasis associated with diminished currents of Nifedipine-sensitive voltage-gated L-type calcium-channels [22]. This finding contradicts another showing that voltage-gated calcium channels are not affected in PrP knockout hippocampal neurons despite exhibiting

impaired slow afterhyperpolarization, suggesting that the disruption of calcium homeostasis is less likely to be due to a dysfunction or loss of voltage-gated calcium channels [10]. In a study by Powell et al., they revealed that the calcium uptake into the ER, a calcium storage mechanism essential for normal cellular calcium homeostasis, was abnormally enhanced in PrP knockout neurons [10]. This dysfunction, together with the reduced amplitude of slow afterhyperpolarization, was significantly rescued following pharmacological inhibition of the sarcoplasmic/ER pump calcium-ATPase [10]. Together, these data suggest that PrPC regulates intracellular calcium homeostasis largely by controlling ER calcium uptake, which subsequently alters the activity of voltage gated calcium channels.

### 2.4 PrPC regulates function of inhibitory neurons

Mice devoid of PrPC expression exhibit weak GABA(A) receptor-mediated fast inhibition in the hippocampal CA1 region [24]. The inhibiting role of GABAergic neurons in the glutamatergic transmission is important to ensure no hyperactivity of the excitatory neurons [39]. This weak GABAergic neuronal activity in the absence of PrPC is consistent with other reports of enhanced excitability in the hippocampal CA1 and dentate gyrus of PrP knockout mice [14, 32, 40]. Importantly, the hyperactivity of excitatory neurons together with the weak function of GABA(A) receptor agrees with the report that PrP knockout mice are susceptible to kainite-induced epileptic seizure [40]. However, a study of the olfactory bulb in PrPC lacking mice has shown an enhanced inhibitory postsynaptic currents are received by mitral cells, which appears associated with the depressed high-frequency oscillations during a single breath [41]. Altogether, PrPC appears to differentially regulate inhibitory neuronal activity based on location; where in the hippocampus it enhances the inhibitory activity to prevent excitotoxic death, the olfactory bulb it prevents hyperactivity of the inhibitory cells to maintain normal high frequency oscillations [41].

### 2.5 PrPC maintains myelination of nerve cells

One of the abnormalities detected in mice lacking PrPC expression is the demyelination of peripheral nerve cells [42]. The loss of PrPC in neurons, but not in Schwann cells, triggers chronic demyelination, which causes significant reduction in peripheral nerve conduction velocity [42]. This dysfunction can be prevented by re-introduction of PrPC expression as well as by activation of PrPC proteolysis [42], thus indicates that PrPC is necessary for maintaining the integrity of myelin sheath. This finding helps consolidating locomotion deficits such as reduced capability to explore an open field, nest, swim, and groom, which have been reported in aged PrP knockout mice [27, 43]. However, it is not yet known whether PrPC also displays this function in the central nervous system.

### 2.6 PrPC regulates major intracellular signaling pathways

PrPC anchoring to the cell membrane is thought to be essential for its role in signaling functions [35, 44]. Several downstream signaling pathways of PrPC have been identified following the discovery of its role as a receptor in neurotoxicity of amyloid beta and alpha-synuclein oligomers [15, 45]. These oligomers bind to PrP residues 95–105 [46] and mediate activation of the signaling intermediate Fyn tyrosine kinase by mGluR5, which causes overactivation of NMDARs leading to excitotoxicity and cell death [15, 45]. Similarly, NMDAR is also overactivated by infectious and toxic PrPD species binding to membrane PrPC, likely through the

same mechanistic pathway as the oligomers of amyloid beta and alpha-synuclein, which subsequently activates the p38 Mitogen Activated Protein Kinase signaling pathway and induces neurotoxicity [23]. The activation of these downstream signaling pathways significantly disrupts both the propagation of action potentials and synaptic functions leading to impairment of LTP and LTD [15, 23, 45, 47, 48]. Together, the evidence suggests that, indirectly, PrPC normally acts as an upstream modulator of a wide variety of intracellular signaling pathways that are essential for neuronal activity.

## 3. Neuro-physiology during prion diseases

Because the underlying mechanisms by which neuronal functions become impaired following the misfolding of PrPC to PrPD and the accumulation of PrPD remain largely unknown, studies have been focused on determining how the roles of PrPC in neuronal activity become altered during disease. However, these mechanisms may be influenced by how PrPC gets misfolded into PrPD. There are three etiologies of prion disease; exposure to infectious prions (acquired), familial disease-related mutations within *prnp*, or undergoing unknown cellular events that cause sporadic prion disease. To date, there has been no way to identify cells that might develop sporadic prion disease due to its unknown cause. However, the causes of acquired and genetic prion diseases can be identified, allowing these diseases to be modeled in the laboratory. These models of prion diseases have provided significant insights to physiological changes in cells prior to clinical onsets.

During the clinical stage of either acquired or genetic prion diseases, significant degeneration of neurons has occurred, as well as the pathological features specific to prion diseases such as spongiosis, deposition of PrPD including the protease-resistant species, and production of potent self-propagating PrPD [49–51]. The degeneration of neurons impedes studies attempting to further understand pathogenic mechanisms during this stage of the disease for two main reasons. Firstly, the degeneration of neurons is almost solely responsible for all neuronal dysfunctions at the clinical stage [51, 52]. Second, neuronal degeneration is irreversible; attempts to rescue mice that have already undergone neuronal degeneration only prolong the disease progression in the terminal stages to death [53]. In addition, recent studies have reported that at the clinical stage of CJD, the peripheral nerves are also severely demyelinated (**Figure 1(6)**) [54, 55], supporting that therapeutic drug interventions at this stage might be too late. Hence, studies have shifted interests toward understanding changes during the preclinical stage to early onset of clinical signs at which points the neurodegeneration is very minimal and therapeutic interventions have been successful in mice [56]. Since electrophysiological paradigms can detect neuronal dysfunctions during the asymptomatic stage as well as the early symptomatic stage, studies have utilized these paradigms to further understand molecular mechanisms that may lead to therapeutic development against neuronal degeneration.

### 3.1 Acquired prion diseases

When mice expressing endogenous PrPC are exposed to infectious PrPD, they will develop prion disease, usually over a well-defined (strain-specific) period of time [57, 58]. Hence, it is possible to study biochemical and physiological properties of mouse neuronal cells during the asymptomatic stage prior to the onset of clinical disease. The hippocampal CA1 LTP is significantly impaired in wild type mice infected with mouse-adapted scrapie (ME7) before the onset of clinical

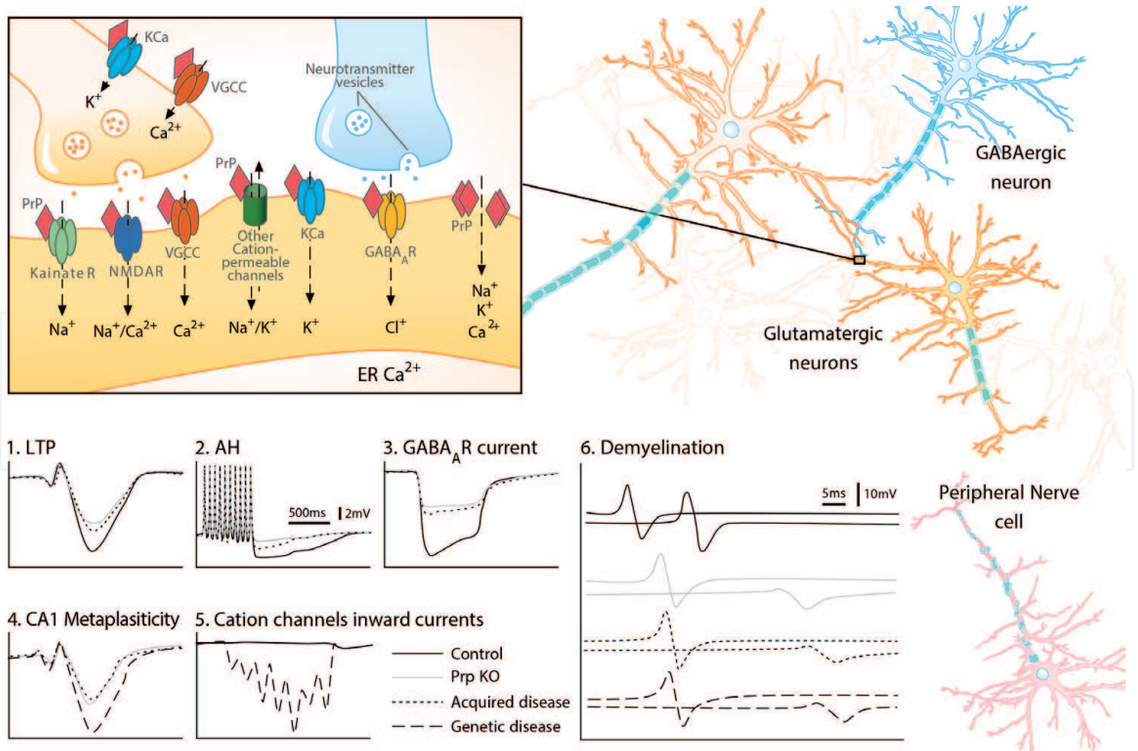


**Figure 1.**
*Connections between the neuro-physiological changes during diseases pathogenesis and the loss or corruption of PrPC function. The neurons in the low magnification (top right side) are CNS neurons with normal myelin sheath. These neurons include two glutamatergic neurons (yellow) and one GABAergic neurons (blue) that form dendrodendritic synapses (as visualized in high magnification). The neuron at the bottom right corner is a peripheral nerve cell with demyelination. Relative to wild type mice expressing PrPC without the disease:* ***1****—hippocampal LTP is impaired in mice lacking PrPC as well as in mice developing prion disease caused by infection;* ***2****—the amplitudes of medium and slow afterhyperpolarizations (AHs) are reduced in PrP knockout (KO) mice and wild type mice during the early symptomatic stage of prion disease caused by exposure to infectious PrPD;* ***3****—GABA(A) receptor currents are weak in PrP knockout mice as well as in disease caused by PrPD infection;* ***4****—hippocampal CA1 metaplasiticity is abnormally enhanced in mice harboring the D178N/129V mutation and slightly enhanced in PrP knockout mice;* ***5****—inward ion currents through cation-permeable channels are abnormally increased in cells expressing P101L, G113V, and G130V;* ***6****—peripheral nerve cells are demyelinated in both PrP knockout mice as well as in disease.* ***1–5****—These dysfunctions are likely due to changes in activities of several key receptors/ion channels, known to interact with PrP, in excitatory (Glutamatergic) and inhibitory (GABAergic) neurons.*

signs (**Figure 1(1)**) [51, 59]. This impairment of LTP strongly correlates with the increased levels of synaptic PrPD [59]. A similar finding has been reported in hamsters infected with hamster-adapted scrapie PrPD (Sc237) [60]. The LTP dysfunction indicates an overall synaptic transmission abnormality (**Figure 1**). Because PrP regulates activities of various receptors in both pre- and postsynaptic terminals that are essential for the induction and maintenance of LTP, the disruption of LTP is likely a result of the functions of these receptors being altered during disease. From as early as 30 days post inoculation (dpi) in the neocortex layer five and 50 dpi in the hippocampal CA1, before the early onset of clinical disease (70–80 dpi), the medium and late afterhyperpolarizations become significantly impaired (**Figure 1(2)**) [60]. This finding suggests a significant calcium dysregulation at this stage of the disease, which is believed to be due to a significant disruption of certain voltage-gated calcium channels such as those activated by potassium or from a significant failure of intracellular calcium storage systems to store or release calcium [60]. In addition, the activity of GABA(A) receptor is hindered in GPI−/− mice infected with scrapie during the early stage of the disease (**Figure 1(3)**) [61]. This finding appears consistent with the reports of the close interaction between GABA(A) receptor and PrPD across the disease progression as well as the increased GABA-like immunoreactivity in various brain regions of scrapie-infected hamsters

starting from 21 dpi [62, 63]. The weak inhibitory activity of GABA(A) receptor may be associated with why seizure is common in prion disease.

Another way of studying the specific effects of exposure to toxic PrPD is through assessing the acute response of cells [5, 64]. A recent study has reported that acute exposure of *ex vivo* hippocampal slices to *ex vivo* mouse-adapted human prions (M1000 and MU02) disrupts CA1 LTP by causing dysfunctions of both pre- and postsynaptic activity [5]. With a similar approach, one study has reported that a 24-hour exposure of a mouse-adapted scrapie (RML) to cultured primary neuronal cells from wild type mice causes reduction of spontaneous neuronal activity due to a substantial loss of dendritic spines [23, 64]. The data show that, prior to developing clinical prion disease, neuronal cells modeling acquired prion disease have already undergone substantial biochemical and physiological changes.

### 3.2 Genetic prion diseases

Genetic prion diseases have been modeled in mice as well as in cultured cells. Genetic prion diseases are caused by disease-related mutations in the *prnp* gene. These diseases are autosomal dominant, therefore only one copy of the mutant allele is required to cause disease. Using these models, cellular and physiological changes can be measured during the asymptomatic stage prior to the onset of clinical signs, or before the misfolded PrPD becomes detectable [29, 65, 66]. Tg(PG14) mice, expressing a nine repeat insertion in the prion octapeptide region, display significant motor deficits prior to neuronal degeneration [65]. These early motor disturbances are associated with poor synaptic transmissions in cerebellar glutamatergic neurons due to a dysfunction in the mechanism that traffics and anchors voltage-gated calcium channels onto the cell membrane [65]. While the mechanisms of these abnormalities are likely due to a loss of functional PrPC or corruption of normal PrPC roles, the peptide insertion may directly yield PrPD species that are neurotoxic, resembling the pathophysiological mechanism of other diseases with repeat insertion such as Huntington's disease. Mouse models of familial CJD (Tg(CJD)) with the D178N mutation and a valine at codon 129, exhibit significant dysfunction of hippocampal CA1 LTP and metaplasticity during the presymptomatic stage (**Figure 1(4)**), which is approximately 50% of the disease progression, to the early onset of clinical disease [29, 66].

In cultured cells, expression of PrP P101L, a point mutant of mouse PrP that is equivalent to P102L mutation in GSS, significantly enhances inward currents and cell death despite a lack of insoluble PrPD (**Figure 1(5)**) [35, 36]. Similarly, cells expressing G113V or G130V mutations (models of genetic CJD and GSS) have minimal levels of insoluble PrPD but display increased inward currents [35]. Based on the role of PrPC as a regulator of ion channel activity (as described previously), the enhanced inward currents are likely due to a loss of PrPC functionality. However, exogenous PrP mutant lacking residues 105–125 while containing the membrane anchor motif can directly mediate membrane pore formation that increases sodium and calcium inward currents [67]. This finding suggests that the PrP mutant directly mediates neurotoxicity. Consistently, one study has revealed that the introduction of nanomolar concentrations of an exogenous PrP mutant lacking the residues 106–126 to rat forebrain neurons enhances the neuronal excitability by disrupting the whole-cell outward potassium currents, including the currents of calcium-activated potassium channels, which subsequently impairs the inhibitory activity of GABA [68]. This finding is consistent with Tg(CJD) mice exhibiting high susceptibility to kainite-induced seizure [65], and the report of carriers of the E200K mutation displaying increased MRI cortical hyperintensity during the early onset of clinical disease [1]. Taken together, PrPD species in genetic prion diseases

appear to cause a significant dysfunction of inward and outward ion currents, which can disrupt the role of inhibitory neurons, thereby leading to enhanced neuronal excitability and consequently cell death.

## 4. Conclusions

PrPC plays a variety of essential roles in neuronal electrical signaling. PrPC maintains electrophysiological phenomena associated with cognition and behaviour by regulating ion channels activity, calcium homeostasis, inhibitory neuronal activity, various intracellular signal transduction pathways, and peripheral nerve myelination. These roles have been determined through two main experimental approaches including (1) knocking out of PrPC expression to completely abolish the roles of PrPC, and (2) deletion of specific PrP amino acid residues to change PrPC functions. Importantly, prior to the overt degeneration of neurons during the disease's progression, some of the disease-related neuronal dysfunctions are very similar to the altered neuro-physiological properties evident when PrPC is abolished or mutated. The reduction of LTP, impaired medium and late afterhyperpolarizations, disrupted calcium homeostasis, and weak inhibitory activity of GABA(A)R (**Figure 1**), are evident in mice devoid of PrPC as well as in mice and rats at the stages (asymptomatic to early onset) of prion diseases caused by exposure to infectious PrPD. In addition, the hyperactivity exhibited by neurons lacking the charged and hydrophobic residues of PrP is also evident in neurons of mice and cells harboring the disease-related mutants such as the D178N/129V and P101L (**Figure 1**). Further, some of the disease-related neuronal dysfunctions such as the reduction of LTP and spontaneous neuronal activity are evident in neuronal cells exposure to neurotoxic PrPD, which indicates that another way PrPC contributes to disease pathogenesis is by gaining a neurotoxic role. Overall, while the specific mechanisms of PrPC and PrPD engagement with the neuronal electrical signaling pathways remain to be elucidated, there are clear connections between the neurophysiological changes during diseases pathogenesis and the loss or corruption of PrPC function.

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## Conflict of interest

Authors declare no "conflict of interest."

## Abbreviations

| | |
|---|---|
| AMPARs | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors |
| CJD | Creutzfeldt-Jakob disease |
| EEG | electroencephalography |
| fMRI | functional magnetic resonance imaging |
| GABARs | gamma-aminobutyric acid receptors |

| | |
|---|---|
| GPI | glycosylphosphadiylinositol |
| GPI−/− | GPI anchorless |
| GSS | Gerstmann-Straussler-Scheinker syndrome |
| KR | kainate receptor |
| KCa | calcium-dependent potassium channel |
| LTD | long-term depression |
| LTP | long-term potentiation |
| MEG | magnetoencephalography |
| NMDARs | N-methyl-D-aspartate receptors |
| PrP | total prion protein species |
| PrPC | normal prion protein |
| PrPD | disease-causing PrP |
| RML | Rocky Mountain Laboratory prion |
| STP | short-term potentiation |

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