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AMPA Palmitoylation Tunes Synaptic Strength: Implications for Synaptic Plasticity and Disease

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Review of Itoh et al.

The addition of lipid moieties to proteins has been studied for nearly 40 years (Folch and Lees, 1951; Kamiya et al., 1978; Schmidt et al., 1979; Carr et al., 1982), but the scope and diversity of functional consequences are still being investigated. This is particularly true for protein palmitoylation, which is a reversible lipid post-translational modification. Palmitoylation entails the addition of a 16-carbon fatty acid, palmitate, to proteins by a class of DHHC-domain-containing proteins called palmitoyl acyltransferase (PATs). These PATs are encoded by the *ZDHHC* gene family (Fukata et al., 2004). Depalmitoylation, on the other hand, is performed by multiple enzyme classes (acyl-protein thioesterases, palmitoyl-protein thioesterases, and the α/β -hydrolase domain 17 proteins) that collectively make up the depalmitoylases (Won et al., 2018). Palmitoylation increases the hydrophobicity of proteins, generally increasing their association with cellular membranes. However, palmitoylation also directs endolysosomal protein sorting, affects protein turnover, and influences protein–protein

interactions, processes critical for synaptic function (Linder and Deschenes, 2007; Fukata and Fukata, 2010; Salaun et al., 2010). Palmitoylation is prevalent on synaptic proteins (Sanders et al., 2015), including crucial synaptic scaffolds and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), which mediate most excitatory synaptic transmission.

AMPA receptors are glutamate-gated ion channels composed of differing combinations of four subunits, GluA1–4 (encoded by *GRIA1–4*), each of which is palmitoylated. GluA palmitoylation occurs at two distinct clusters: within the second transmembrane domain (TMD2) and at the C terminus in the juxtamembrane domain near the fourth TMD (TMD4) (Hayashi et al., 2005). Palmitoylation of GluA1 at TMD2 is mediated by the Golgi-resident PAT, DHHC3, and it promotes GluA retention in the Golgi. Hence, mutations that prevent palmitoylation of TMD2 increase expression of GluA1 in the plasma membrane. In contrast, C-terminal palmitoylation does not influence basal surface expression of AMPARs (Hayashi et al., 2005). Instead, acute glutamate exposure causes the depalmitoylation of GluA1 at the C terminus, demonstrating that this site is responsive to synaptic activity. These results indicate that palmitoylation of GluAs regulates their surface expression at baseline and may impact synaptic plasticity.

Regulated synaptic plasticity is critical for appropriate neuronal communication in health and disease (Bliss et al., 2014). LTP and LTD are two prominent forms of synaptic plasticity that often involve, respectively, the addition and removal of AMPARs from synaptic sites (Huganir and Nicoll, 2013). Importantly, GluA1-containing AMPARs that lack GluA2 are permeable to calcium, distinguishing them from other AMPAR species (Diering and Huganir, 2018). This distinction has led to intense study surrounding the role of GluA1 in synaptic plasticity and its regulation by post-translational modifications. Indeed, GluA1 expression and phosphorylation of the C-terminal tail are necessary for some forms of plasticity (Jensen et al., 2003; Goel et al., 2011; Zhou et al., 2018). Further, dysregulation of GluA1 or altered post-translational modification of its C terminus is implicated in neurological disorders, including epilepsy (Zhang and Abdullah, 2013; Yang et al., 2018). However, little is known about the role of GluA1 palmitoylation in these processes.

In a recent study, Itoh et al. (2018) investigated the effect of GluA1 palmitoylation on AMPAR function at hippocampal synapses *in vivo*. Specifically, AMPAR-mediated synaptic transmission and plasticity were examined in knock-in mice, in which the C-terminal palmitoylation site of GluA1 (a cysteine at residue 811) was replaced by serine (C811S), thus

Received Jan. 8, 2019; revised April 18, 2019; accepted April 20, 2019.

I thank my mentor, Dr. Akira Yoshii, and the Graduate Program in Neuroscience at the University of Illinois at Chicago for supporting my writing of this commentary.

The authors declare no competing financial interests.

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<https://doi.org/10.1523/JNEUROSCI.0055-19.2019>

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prohibiting palmitoylation. Basal measures of AMPAR function were comparable between WT and homozygous mutant (CS/CS) mice, corroborating previous results demonstrating that C-terminal palmitoylation is dispensable for AMPAR trafficking at baseline (Hayashi et al., 2005). Furthermore, induction of LTP by electrical stimulation (4 trains of 100 Hz) and induction of LTD by bath application of NMDA (30 min) were normal at CS/CS synapses, indicating that C-terminal palmitoylation is not required for these forms of plasticity. In contrast, chemical LTP (cLTP) induced by 30 min bath application of the NMDAR coagonist glycine and the GABA_A receptor antagonist picrotoxin was amplified in CS/CS hippocampal neurons, as suggested by greater increases in the volume of dendritic spines. This suggests that GluA1 C811 palmitoylation restricts synaptic AMPAR insertion to limit the extent of synaptic potentiation during cLTP, which may be important for dampening neural excitability in response to strong stimulation (Itoh et al., 2018).

To test this hypothesis, the authors examined whether altered GluA1 palmitoylation affected seizure susceptibility after treatment with pentylenetetrazole (PTZ, a noncompetitive GABA_A receptor antagonist), a model of epilepsy. Administration of a single dose of PTZ caused a greater increase in the number of tonic-clonic seizures in CS/CS mice compared with WT. Notably, with repeated (every 48 h for 12 doses) PTZ treatment, induction of severe seizure (tonic-clonic) activity required fewer doses of PTZ in CS/CS mice, and seizure events were prolonged compared with WT. These data suggest that CS/CS mice are sensitized to recurrent seizures caused by PTZ administration. Furthermore, PTZ-induced seizures in CS/CS mice were resistant to treatments with multiple antiepileptic drugs that potentiate inhibitory (i.e., GABAergic) neurotransmission, such as valproic acid, phenobarbital, and diazepam (Itoh et al., 2018). Together, the evidence provided by Itoh et al. (2018) supports a role for synaptic GluA1 palmitoylation in the dampening of synaptic potentiation (cLTP) that may be important for protection from seizure.

Still, the mechanism by which cLTP is potentiated in CS/CS mice remains unknown. Itoh et al. (2018) note that phosphorylation of GluA1 S831, but not S845, was increased at baseline in CS/CS neurons; a third site, S818, was not examined (Itoh et al., 2018). Generally, phosphory-

lation at these sites promotes GluA1 surface expression during LTP (Diering and Hugarir, 2018). However, mutations that eliminate phosphorylation of either S831 or S845 alone do not impair hippocampal LTP (Lee et al., 2010), and S831 is not required for synaptic GluA1 delivery after LTP induction (Hayashi et al., 2000). Further, it has been explicitly suggested that S845 may play a permissive or priming role in LTP (Oh et al., 2006; Lee and Kirkwood, 2011). In contrast, mutations blocking the phosphorylation of S818 cause deficits in the synaptic targeting of GluA1 and hippocampal LTP (Boehm et al., 2006). In addition, blocking S818 phosphorylation can occlude the effects of phosphorylation at other sites (Boehm et al., 2006). Therefore, while S831 and S845 phosphorylation act to enhance LTP under some circumstances, phosphorylation of GluA1 at S818 more directly influences synaptic AMPAR insertion during LTP (Boehm et al., 2006; Lee and Kirkwood, 2011). Importantly, C811 palmitoylation inhibits S818 phosphorylation (Lin et al., 2009). Moreover, C811 palmitoylation blocks the interaction between GluA1 and the protein 4.1N, which typically stabilizes AMPARs at the synaptic surface during LTP (Lin et al., 2009). Thus, lack of GluA1 depalmitoylation may facilitate robust phosphorylation at S818 and interaction with 4.1N, thereby enhancing the synaptic targeting of S818/S831-phosphorylated GluA1 during cLTP in CS/CS neurons.

While progress has recently been made identifying the PATs that mediate steady-state and activity-dependent palmitoylation of synaptic proteins, including AMPARs (Noritake et al., 2009; Fukata et al., 2013; Brigidi et al., 2015; Tabaczar et al., 2017), less is known about the enzymes that depalmitoylate them. However, a clue might come from the finding by Itoh et al. (2018) that the greatest increases in dendritic spine size following cLTP occurred in large spines of CS/CS neurons. This suggests that the role of GluA1 C811 palmitoylation is emphasized at these large synapses. Large, mature dendritic spines preferentially contain satellite extensions of smooth endoplasmic reticulum called the spine apparatus, as well as Golgi membranes (Spacek and Harris, 1997; Pierce et al., 2001; Mikhaylova et al., 2016), suggesting that a Golgi resident might depalmitoylate AMPARs at mature synapses. The acyl-protein thioesterases (APTs, APT1, and APT2) shuttle between the Golgi and cytosol in peripheral cell types; and notably, ongoing APT1 activity is required to

maintain voluminous dendritic spine morphology in rat hippocampal neurons (Siegel et al., 2009). Furthermore, APT1 expression is rapidly suppressed after cLTD induction, suggesting that postsynaptic reduction of APT1 levels may contribute to the surface AMPAR removal characteristic of LTD (Siegel et al., 2009; Antoniou et al., 2014; Rajgor et al., 2017). Together, these data imply that APTs may depalmitoylate AMPARs during synaptic plasticity. However, two additional depalmitoylases may act on GluA1: the α/β hydrolase domain-containing proteins 17A-C, recently identified depalmitoylases for PSD-95 and other neuronal proteins, and palmitoyl-protein thioesterase 1, which affects the palmitoylation state of postsynaptic NMDA receptors (Lin and Conibear, 2015; Yokoi et al., 2016; Koster et al., 2019). Whether these enzymes act on GluA subunits, however, is incompletely studied. Defining which depalmitoylases are active at the synapse and how they regulate synaptic proteins are a crucial next step toward a more comprehensive picture of synaptic plasticity mechanisms.

It is not immediately clear why palmitoylation-deficient GluA1 would potentiate cLTP but not electrically stimulated LTP. Importantly, the synaptic incorporation of GluA1-AMPA receptors following electrically evoked LTP is the subject of debate (Plant et al., 2006; Adesnik and Nicoll, 2007), whereas the cLTP protocol used is recognized to reliably induce GluA1 incorporation (Musleh et al., 1997; Lu et al., 2001). Furthermore, Itoh et al. (2018) measured evoked LTP using field recordings, which are the sum of activity at many synapses. Because the effects of C811S mutation during cLTP were observed in a subpopulation of individually monitored spines, they might have been lost in population recordings. Thus, cLTP paired with the imaging protocol used may have been better suited to detect alterations in plasticity related to synaptic GluA1 trafficking in CS/CS neurons. Although Itoh et al. (2018) did not directly examine changes in the surface AMPAR population induced by cLTP, and GluA1 trafficking can be uncoupled from changes in spine size during synaptic plasticity (He et al., 2011). An alternate possibility, therefore, is that C-terminal GluA1 palmitoylation preferentially regulates structural plasticity (spine size) during cLTP in mature spines. Thus, further experiments are warranted to dissect the precise role of GluA1 C-terminal palmitoylation during LTP and elucidate the

therapeutic value of targeting GluA1 palmitoylation in epilepsy.

Current antiepileptic drugs either suppress neuronal excitation or potentiate inhibitory neurotransmission to reduce the occurrence of seizures; however, seizure relapse or development of drug-resistant epilepsy is common for up to 1 in 3 patients (Schmidt and Löscher, 2005). Itoh et al. (2018) demonstrate that seizures in CS/CS mice are resistant to antiepileptic drugs that enhance GABAergic neurotransmission (valproic acid, phenobarbital, diazepam), implying that the surface expression of AMPARs is a barrier to the efficacy of these drugs. Whether inhibiting AMPARs directly using peramppanel, an AMPAR antagonist approved for epilepsy treatment, would have proved more efficacious in CS/CS mice is unclear, but it is an intriguing possibility. Performing such experiments might illustrate that epileptic activity driven by AMPAR dysfunction (e.g., as in CS/CS mice) is resistant to compensatory treatments to increase GABAergic signaling. That is, correcting the balance between excitation and inhibition may be insufficient to fully reverse epileptic activity in some cases; instead, targeting the receptor subsystem underlying neural hyperexcitability may be necessary to achieve better treatment outcomes. Targeting AMPAR palmitoylation, therefore, might broaden the therapeutic range to circumvent limitations of conventional antiepileptic drugs and provide therapeutic value for epilepsy (Yang et al., 2018).

Beyond epilepsy, palmitoylating and depalmitoylating enzymes are implicated in schizophrenia (Mukai et al., 2004, 2008), Huntington's disease (Yanai et al., 2006; Milnerwood et al., 2013; Sutton et al., 2013), infantile neuronal ceroid lipofuscinosis (Vesa et al., 1995), and cancer (Hernandez et al., 2017; Mohammed et al., 2019; Sadeghi et al., 2018). Mutations affecting the palmitoylation state of neuronal proteins cause severe neurodegenerative phenotypes and other disorders (Yanai et al., 2006; Nosková et al., 2011; Cho and Park, 2016). Also, the dysregulated palmitoylation of proteins is implicated in various diseases, including Alzheimer's disease (Cho and Park, 2016). Thus, palmitoylation is a robust regulator of disease-relevant proteins that may provide various novel therapeutic opportunities. Targeting palmitoylation has already proven valuable in preclinical models of cancer (Hernandez et al., 2017; Lin et al., 2017; Mohammed et al., 2019; Nicastri et al., 2018) and neurological diseases di-

rectly born from deficits in the palmitoylation machinery (Sarkar et al., 2013). However, the promiscuity of current palmitoylation and depalmitoylation inhibitors limit their therapeutic value. To overcome this issue, improved pharmacological tools are being generated to target palmitoylating and depalmitoylating enzymes, which will improve the specificity with which the palmitoylation state of proteins is altered and limit off-target effects (Draper and Smith, 2009; Dekker et al., 2010; Hamel et al., 2016; Vujic et al., 2016; Nicastri et al., 2018). These tools and others (e.g., genetic techniques) are accelerating the identification of disease-relevant PATs, such as DHHC17 in Huntington's disease (Young et al., 2012), and depalmitoylases, such as palmitoyl-protein thioesterase 1 in cancer (Rebecca et al., 2017). As a higher-resolution landscape of the PATs and depalmitoylases that affect critical proteins emerges, novel therapeutic strategies will likely be revealed for palmitoylation-related diseases and neurological disorders more generally.

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