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Protein Kinases in Spinal Plasticity: A Role for Metabotropic Glutamate Receptors

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1. Introduction

Neural plasticity is characterized by the lasting modulation of synaptic strength which alters the central nervous system's (CNS) capacity to encode and store information. Changes in synaptic plasticity have implications for brain-dependent learning and memory as well as a number of other forms of CNS information processing, including alterations in spinal cord function (reviewed in Patterson & Grau, 2001). As protein kinases have been shown to greatly affect neurotransmitter receptor dynamics, their role in synaptic plasticity is essential. A large body of work has highlighted the link between group I metabotropic glutamate receptor (mGluR) activation, subsequent protein kinase activation, and synaptic plasticity (Gereau & Heinemann, 1998; Sheng et al., 2002; Gallagher et al., 2004). Upon glutamate binding to mGluRs, a G-protein coupled to the receptor sets off an intracellular cascade, activating phospholipase C (PLC), diacyl glycerol (DAG), and ultimately protein kinases. Once activated, protein kinases can then exert a modulatory effect on both excitatory and inhibitory receptors that ultimately affects synaptic strength. In this way, mGluRs and protein kinases both play critical roles in a number of forms of neural plasticity, including those that are thought to underlie learning and memory (Bortolotto & Collingridge, 1993; Wang, et al. 2004). What many in neuroscience have overlooked is the fact that, just like in the brain, the *spinal cord* also exhibits the capacity for an amazing amount of plasticity, including simple forms of learning and memory that are relevant to pain, motor learning, and recovery of function after spinal cord damage (Woolf & Salter, 2000; Grau et al., 2006; Raineteau & Schwab, 2001). And, just as in the brain, spinal plasticity has been shown across a number of preparations to be mediated by mGluR/protein kinase signaling (Giles et al., 2007; Ferguson et al., 2008a).

This chapter will detail the specific role of protein kinase C (PKC) as an intermediary between initial mGluR activity and long-term changes in synaptic strength, and how this critical interaction affects a number of spinal processes. We will highlight how PKC and its isoforms provide a critical link between initial glutamatergic input and the alterations in receptor phosphorylation and trafficking that lead to spinal plasticity. We will first look at the role of mGluR/PKC signaling in the dorsal horn of the spinal cord, and the implications of this process on pain. We will then explore how the mGluR/PKC pathway also exerts modulatory control over the changes in plasticity (or *metaplasticity)* in the spinal cord, as evidenced in a spinal cord learning preparation. In addition, we will consider how the

reorganization and reclamation of appropriate function after spinal cord injury is affected in large part by various forms of mGluR-mediated, protein kinase-dependent plasticity. Finally, we will investigate the neurobiological consequences and possible therapeutic potential to be found in altering protein kinase activity.

2. Nociceptive plasticity: mGluRs, protein kinase C, and pain

mGluR-mediated activation of protein kinases can modulate synaptic strength, by altering presynaptic and postsynaptic signaling. While these forms of synaptic plasticity have been suggested to underlie learning and memory in the hippocampus, similar mechanisms at work in the dorsal horn of the spinal cord produce a decidedly different form of learning that contributes to neuropathic pain. As the dorsal horn is the locus for the integration of incoming sensory information, sensitization of these neurons and their synaptic targets can have a dramatic behavioral effect (Mendell, 1966; Woolf, 1983). If a strong nociceptive signal is relayed from the periphery to the superficial dorsal horn, neurons in this area become sensitized, in a fashion that is mechanistically very similar to long-term potentiation (LTP), an electrophysiological mechanism believed to underlie learning and memory in the hippocampus (Sandkuhler & Liu, 1998; Bliss & Collingridge, 1993). This effect has been termed *central sensitization* (Woolf, 1983). As in any form of potentiation, subsequent input following sensitization can elicit a response even if it is much weaker than the initial input. That is, even those stimuli that would not normally be considered painful may now have the capacity to elicit a nociceptive response (*allodynia*). Likewise, normally painful stimuli can now induce a much more robust nociceptive response (*hyperalgesia*). These phenomena are conserved across species, and this makes sense from an evolutionary standpoint. To be rapidly sensitized to a painful stimulus is indeed adaptive, in that an organism will 'learn' to avoid this stimulus. Although this type of plasticity is essential for self-preservation, it can be problematic if dysregulated. Neural insult, whether it be an injury to the peripheral nervous system (e.g., nerve damage) or central nervous system (e.g., spinal cord injury), can produce an unregulated barrage of nociceptive input that may have no external initiator. This can produce a persistent pain response, and lasting nociceptive plasticity, that is generated wholly within the organism (neuropathic pain) (Kim & Chung, 1992; Christensen & Hulsebosch; Willis & Coggeshall, 1991; Willis & Westlund, 1997; Lindsey et al., 2000). A number of studies have outlined an important role for spinal protein kinase C (PKC) in mediating persistent pain states, including hyperalgesia, allodynia, and neuropathic pain (Coderre, 1992; Sun et al., 2004; Hua et al. 1999). As a major activator of PKC, group I mGluRs have been implicated as a driver of nociceptive plasticity (Yashpal et al., 2001; Fisher & Coderre, 1996; Adwanikar et al., 2004).

mGluRs activate PKC in two ways: both directly, through the G-coupled protein-PLC-DAG pathway, as well as indirectly by freeing intracellular Ca^{++} via activation of phosphoinositide-3 kinase (PI3K) pathway. *In vitro* work has shed light on how PKC works to sensitize spinal neurons and elicit persistent nociceptive behavior. PKC appears to have the capacity to induce sensitization through both presynaptic and postsynaptic effects. Presynaptically, PKC has been shown to phosphorylate voltage-gated calcium channels, thus increasing intracellular calcium and promoting neurotransmitter release (Yang et al., 2005). Postsynaptically, PKC can facilitate excitatory tone through actions on ionotropic glutamate receptors (Lu et al., 1999; Li et al., 1999). Following post-synaptic binding of

glutamate to mGluRs, and subsequent PKC activation, PKC then phosphorylates NMDA receptors, increasing their open probability (Liao et al., 2001). Further, PKC has been shown to induce the rapid exocytosis of AMPA receptors (Li et al., 1999). Taken together, these excitatory effects have been suggested to play a critical role in sensitizing dorsal horn neurons (Ji et al., 2003).

In the brain, however, mGluR activation can have contradictory effects. For example, in hippocampal culture, mGluR activation has been shown to cause *internalization* of AMPA receptors leading to long-term *depression* (LTD) of postsynaptic potentials rather than sensitization (Huber et al., 2000; Oliet et al., 1997; Moult et al., 2002). This effect has been shown to depend on activation of the immediate early gene Arc/Arg 3.1 (Waung et al., 2008) as well as PKC (Camodeca et al., 1999; Oliet et al., 1997). On the other hand, mGluR-induced activation of PKC has also been implicated in LTP (Jia et al., 1998; Balschun et al., 1999; Aiba, et al., 1994; Conquet et al., 1994; Bortolotto, et al., 1994; Anwyl et al., 2009). This confusion about the bi-directional role of mGluRs and downstream PKC in hippocampal-dependent synaptic plasticity has been reviewed elsewhere (Bortolotto et al., 1999; Malenka & Bear, 2004) and the role of mGluRs in LTP and LTD remains a topic of ongoing research in the hippocampal plasticity literature (Mockett et al., 2011). It is clear that much more work is required to reconcile the hippocampal literature with the spinal plasticity literature regarding mGluR-PKC activation.

Tests of the necessity of mGluRs and PKC *in vivo* have confirmed the critical role of this pathway in spinally-mediated nociceptive plasticity. In order to study persistent inflammation, researchers will often give a subcutaneous injection of a noxious substance to the periphery, and then assess the effect this treatment has on the activity of dorsal horn neurons within nociceptive fields (Harris & Ryall, 1988; LaMotte et al., 1992). To investigate the specific role of mGluRs on this type of nociceptive plasticity, Young et al. (1995) gave an injection of the noxious substance algogen (mustard oil) to the hindpaws of rats, a substance known to evoke sustained activity in neurons of the dorsal horn. This treatment was followed by microinjections of the mGluR antagonist CHPG directly into the dorsal horn. They found that blocking mGluR activity with CHPG strongly inhibited mustard oil-evoked activity in these nociceptive areas. Beyond the necessity for mGluRs in sustained nociceptive activity, they also demonstrated the sufficiency for an mGluR agonist (ACPD) to *produce* sustained activity in these neurons (Young et al., 1995). Interestingly, Munro et al. found that treatment with a PKC inhibitor (chelerythrine or GF109203X) was able to inhibit both mustard oil- and ACPD-evoked activity (Munro et al. 1994). Together, these findings provide a strong case for mGluR/PKC signaling in mediating at least one form of long-term nociceptive plasticity. In 2001, Yashpal and colleagues demonstrated a further role for mGluR/PKC interaction in chronic neuropathic pain. Following a chronic constriction of the sciatic nerve (known to produce long-term nociceptive activity in the dorsal horn), they found that membrane localization of PKC was increased. Behaviorally, such an injury manifests as a chronic and robust hypersensitivity to both touch (mechanical allodynia) and temperature (thermal hyperalgesia). But, if an mGluR inhibitor was given prior to and after the injury, they found a decrease in the membrane-bound PKC expression, as well as a decrease in the subjects' injury-induced mechanical and thermal hypersensitivity.

Based on the mechanistic similarities, many researchers have drawn the distinct parallels between learning/memory and pain (Sandkuhler, 2000; Ji et al., 2003; Latremoliere and

Woolf, 2009). It is perhaps not surprising then that recent breakthroughs in our understanding of long-term memory storage in the brain continue to shed light on persistent pain syndromes that are mediated by the spinal cord. The protein kinase PKMζ (an isoform of PKC) is unique in that, unlike most enzymes, it can remain active for extremely long periods of time. This persistence is possibly due to the fact that activated PKMζ inhibits the protein PIN1, an inhibitor of PKMζ mRNA translation. Thus, by blocking the action of its regulator, PKMζ effectively creates a positive feedback loop, perpetuating PKMζ activity (Sacktor, 2011). Once PKMζ becomes active, it can promote trafficking of the major fast excitatory ionotropic glutamate receptor (AMPAR) to post-synaptic membranes, which in turn aids in potentiating the synapse (Sacktor, 2008; Migues et al., 2010; Malinow & Malenka, 2002). Further, PKMζ has been shown to also *inhibit* the internalization of these trafficked AMPARs (Yao et al., 2008). In this way, synaptic strength is not only induced, but also *maintained*. This finding has led many to investigate PKMζ has a critical component in long-term memory. Researchers have found that inhibiting PKMζ produces profound behavioral effects. A number of recent studies have shown that treatment with a PKMζ inhibitor effectively eliminates long-term memories from a number of learning paradigms (Pastalkova et al., 2006; Shema et al. 2007; Parsons & Davis, 2011; Madronal et al., 2010).

While these findings provide compelling evidence for the necessity for PKMζ in long-term memory, erasing long-term memories may not be a likely sought-after therapy. But consider the problem of chronic pain. As we have discussed, long-term neuropathic pain bears a striking mechanistic resemblance to memory, yet it is often regarded to be biologically dysfunctional. Therefore, inhibiting PKMζ may prove to be a very attractive therapeutic tool in overcoming persistent neuropathic pain. Asiedu and colleagues have recently shown this idea to be entirely possible. They initially primed rat subjects with a peripheral intraplantar injection of the inflammatory cytokine IL-6 or vehicle to the hindpaw. This treatment has previously been shown to induce allodynia for up to 3 days after injection (Asiedu et al., 2011). They then injected the mGluR agonist DHPG intrathecally to the spinal cord 6 days after initial peripheral injection, and found that DHPG injection produced a markedly enhanced nociceptive response in those subjects that had been primed days earlier with IL-6. This finding suggested that the maintenance of peripheral nociceptive sensitization was mediated centrally in the spinal cord and led them to investigate the possibility that PKMζ might mediate the storage of this nociceptive 'memory'. They found that intrathecal administration of the PKMζ inhibitor ZIP attenuated the capacity for DHPG to evoke the expression of nociceptive behavior. This lends support for the argument that, as in learning and memory in the brain, this persistent nociceptive sensitization reflects an LTP-like mechanism. Given that PKMζ has been shown to maintain LTP by inhibiting the internalization of AMPARs, and this effect can be disrupted by the peptide pep2m (Yao et al. 2008), Asiedu and colleagues hypothesized that this same mechanism is involved in the maintenance of nociceptive hypersensitivity. To test this, they gave an intrathecal injection of pep2m, and found that this treatment also blocked the DHPG evoked expression of sensitization (Asiedu et al., 2011). Together these findings suggest that the maintenance of nociception involves a PKMζ-dependent process within the spinal cord, and lends confirmatory evidence that the maintenance of LTP, memory, and nociception may be mediated by a common mechanism. In the future, PKMζ inhibition could hold very promising therapeutic potential for those suffering from chronic pain.

3. Learning in the spinal cord: Metaplasticity is PKC-dependent

The spinal cord supports a number of other forms of plasticity beyond just nociception. Throughout development, ventral motor neurons undergo a great amount of plasticity, as complex motor skills and locomotion are honed. Although the spinal cord was once believed to be fairly hard-wired after development, we now understand that the capacity for ongoing plasticity in spinal motor neurons persists throughout life (Edgerton et al. 2001; Courtine et al. 2008; De Leon et al. 2001; Wolpaw, 2007; Grau et al., 2006). This is evident in the spinal cord injury literature from the previous decade, where researchers have demonstrated the ability for spinal cord injured-subjects to regain locomotor function through the use of behavioral training, often in combination with pharmacological agents that facilitate plasticity (Wernig et al., 2000; Rossignol, 2007; Edgerton & Harkema, 2011). Promoting this kind of adaptive, use-dependent spinal plasticity is essential in order to realize functional recovery after injury.

Despite advances in our awareness of the spinal cord's capacity for plasticity, the underlying mechanisms dictating use-dependent spinal cord plasticity still require investigation. In order to better understand the unique role of the spinal cord in neural plasticity, outside of any supraspinal input, researchers have developed an *in vivo*, behavioral method for measuring plasticity in the isolated spinal cord. Building upon earlier work from Chopin and Buerger, Grau and colleagues demonstrated that following a complete spinal transection, spinal neurons below the lesion were able to support a simple form of instrumental (response-outcome) learning (Buerger and Fennesey, 1970; Chopin & Buerger, 1976; Grau et al., 1998). In this preparation, transected rats receive an electrical shock to the tibilias anterior muscle of their hindlimb whenever that limb is in an unflexed position (see Figure 1A). This stimulation causes a flexion of the hindlimb, at which point the stimulation is terminated. When the limb again falls to a resting, unflexed position, another shock is delivered.

Without input from the brain, spinalized subjects will learn to keep the hindlimb flexed in order to reduce exposure to the stimulation (Fig 1C). This form of spinal learning can also be inhibited: if subjects are given electrical stimulation that is not contingent upon limb position (*intermittent stimulation*), they will later fail to learn to keep their hindlimb flexed when tested with response-contingent stimulation (*controllable stimulation;* Figure 1B; Crown et al., 2002). Although these subjects are not learning the target response, they are still exhibiting a form of plasticity. Essentially, they have *learned* from the exposure to intermittent stimulation, that their limb position is not related to stimulation exposure, and thus fail even when later tested with controllable stimulation. This phenomenon has been considered analogous to the phenomenon of *learned helplessness* (Grau et al., 1998; Seligman & Maier, 1967). In contrast to the maladaptive effects of intermittent stimulation, training with controllable stimulation can *enhance* future learning (Grau et al., 1998). Subjects that have previously learned this instrumental task can be tested in the future with a more difficult response criterion (one that untrained subjects would not be able to exhibit), and this prior training *facilitates* learning. While both the learning deficit and the facilitation of learning are forms of plasticity, they are something more. Both of these phenomena affect lasting *change* in plasticity: a lasting alteration in the threshold at which learning occurs, either shifting the threshold up (in the case of intermittent stimulation inducing a future learning deficit) or down (in the instance of instrumental training facilitating future

learning). In essence, these experience-dependent spinal changes represent a *plasticity* of plasticity. Abraham and Bear (1996) first described this type of plasticity of plasticity, characterizing it as "a higher-order form of synaptic plasticity" that they termed *metaplasticity* (Abraham and Bear, 1996). Uncontrollable stimulation induces a lasting alteration that undermines spinal learning, that can be described as a metaplastic inhibition of adaptive plasticity. Importantly, the same stimulation parameters that induce spinal learning deficits also undermine long-term recovery of locomotor function following a spinal contusion injury (Grau et al., 2004). Thus, a better understanding of the neurobiology underlying metaplastic inhibition of adaptive plasticity in the spinal cord will aid in the development of strategies to aid in functional recovery after spinal cord injury.
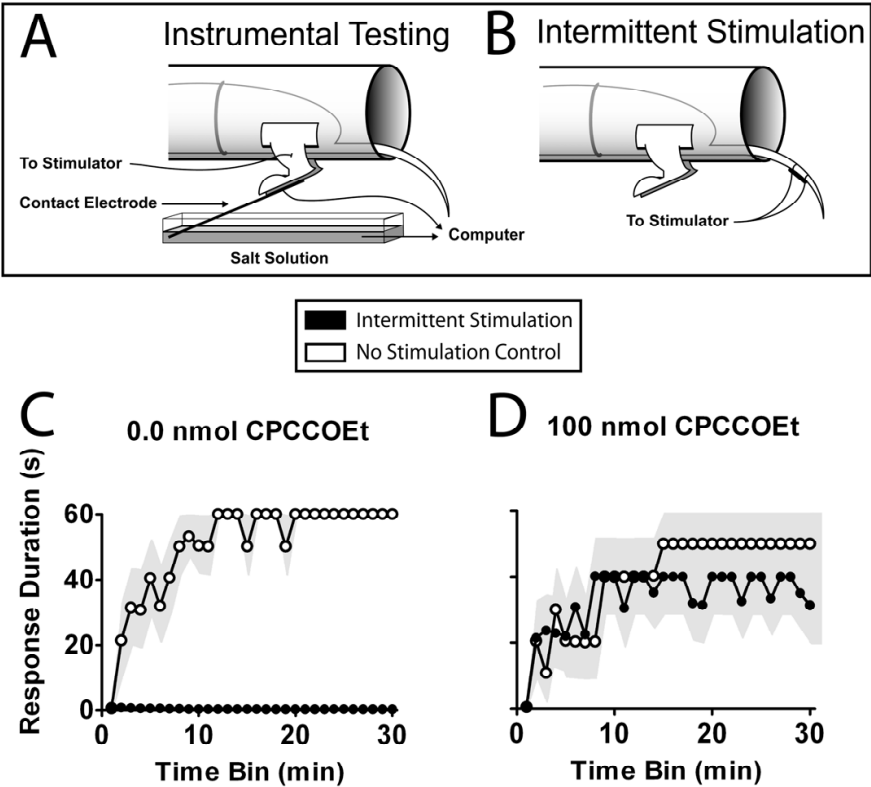

Fig. 1. Instrumental learning model of spinal plasticity, and the role of mGluRs in this phenomenon. A) Spinalized rat subjects are given an electrical shock each time their hindlimb is in an unflexed position (*controllable stimulation*). Over time, they learn to increase their response durations in order to reduce exposure to the stimulation, thus encoding an instrumental (response-outcome) relationship. B) If uncontrollable, intermittent stimulation is administered prior to instrumental testing, the subjects are unable to learn the relationship. C) In subjects that are given vehicle treatment (0.0 nmol of mGluR antagonist CPCCOEt), intermittent stimulation produces a significant spinal learning deficit. D) Treatment with 100 nmol CPCCOEt blocks the deficit induced by intermittent stimulation, suggesting a necessary role for mGluR activity in this effect. Adapted from Ferguson et al., 2008a.

Previous work has shown that metaplasticity in the hippocampus involves ionotropic glutamate receptor trafficking (Hellier et al., 2007). Given that mGluRs modulate ionotropic receptor function and trafficking through a PKC-mediated mechanism, we recently investigated the role of this mechanism in the metaplastic inhibition of spinal instrumental

learning (Ferguson et al., 2008a). We first tested whether group I mGluRs are necessary for the metaplastic inhibition of spinal learning. We found that intermittent stimulation had no effect on future spinal learning if given after an intrathecal injection of an mGluR antagonist (CPCCOEt or MPEP, Fig. 1D). We next considered the contribution of PKC to this learning deficit. We found that in response to intermittent stimulation (which produces a lasting metaplastic inhibition of spinal learning) PKC activity in the spinal cord was significantly increased (Figure 2A). Similarly, if PKC inhibitors (bisindolylmaleimide or chelerythrine) were delivered intrathecally prior to intermittent stimulation, subjects exhibited no metaplastic inhibition of learning when tested 24 hours later. These data provided strong evidence that both mGluR and PKC activity are necessary in producing this form of spinal metaplasticity. To further examine the role of mGluR/PKC in this phenomenon, we tested whether pharmacological activation of mGluRs was sufficient to produce metaplastic inhibition of spinal learning. We found that a single bolus of the mGluR agonist DHPG was able to produce a spinal learning deficit that lasted at least 24 hours. We also found that PKC activity blockade (with chelerythrine or bisindolylmaleimide) prior to administration of DHPG, prevented metaplastic inhibition of spinal learning. These findings suggest an essential role for the mGluR/PKC pathway in mediating metaplasticity in the spinal cord.
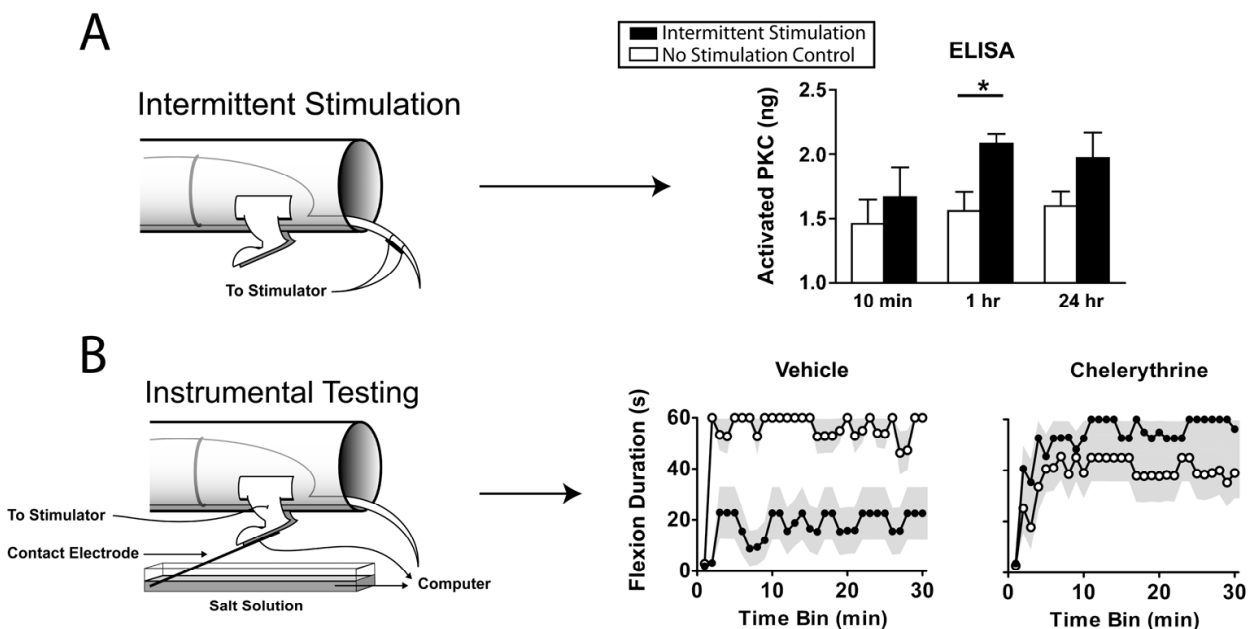

Fig. 2. Role for PKC in the metaplastic inhibition of spinal learning. A) Intermittent stimulation (which induces a lasting metaplastic inhibition of spinal learning) produces an increase in the expression of activated PKC that is significantly greater than unstimulated controls at 1 hour. B) When tested for spinal instrumental learning, vehicle-treated subjects that had received intermittent stimulation fail to learn; intrathecal injection of the PKC inhibitor chelerythrine blocks intermittent stimulation from producing a learning deficit. Adapted from Ferguson et al., 2008a.

As discussed above, PKC is known to alter the open-channel probability of NMDARs. Spinal learning, like many other forms of plasticity, has been characterized by its dependence on subtle, precise alterations in NMDAR function. Thus, it is likely that increased potentiation of NMDARs by the mGluR/PKC pathway upsets a delicate balance, pushing NMDARs (and

subsequent intracellular calcium levels) beyond the range in which spinal learning can occur. Other work has also implicated other protein kinase activity in both the adaptive and maladaptive metaplastic changes in spinal learning. Inhibition of calcium/calmodulin-dependent protein kinase II (CaMKII) has been shown to block the development of the long-term inhibition of spinal learning if given after uncontrollable shock, and also blocks the facilitation effect of instrumental training if given prior to training (Baumbauer et al., 2007; Gomez-Pinilla et al., 2007). These findings suggest that protein kinase activity may engage a common mechanism in different forms of spinal metaplasticity. Future work will be necessary to elucidate how the various protein kinases interact and integrate to produce these lasting behavioral changes. Further, if these mechanisms are at work in the injured spinal cord, we can begin to develop therapeutic strategies that can reduce maladaptive metaplasticity, and promote the adaptive plasticity necessary for successful rehabilitation.
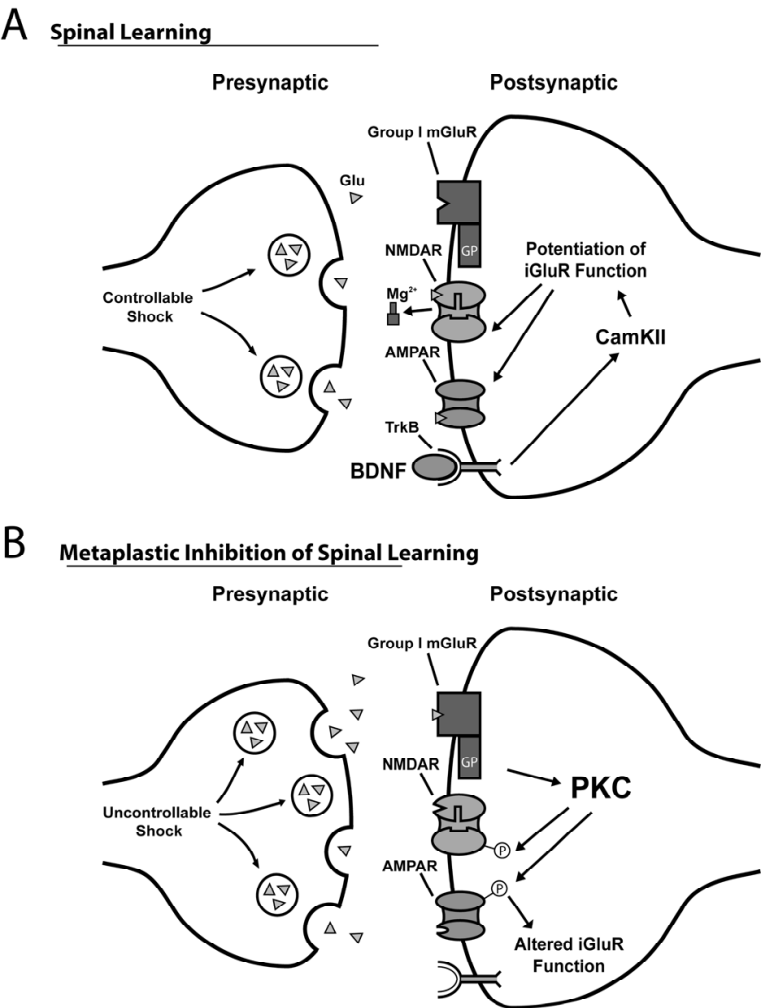

Fig. 3. Possible cellular mechanism for A) spinal learning and B) metaplastic inhibition of spinal learning. Both forms of spinal plasticity have been shown to involve protein kinase signaling. In contrast to controllable stimulation, uncontrollable stimulation is believed to engage group I metabotropic glutamate receptors, which leads to the downstream activation of PKC. PKC in turn alters ionotropic glutamate receptor function, which is believed to induce a lasting saturation of the synapse, inhibiting future learning. Adapted from Ferguson et al., 2008a.

4. Spinal cord injury: Protein kinase modulation as therapy

The previous sections have focused on spinal plasticity in isolated systems: how the mGluR/PKC pathway modulates nociceptive processing in the dorsal horn, and how it mediates the metaplastic inhibition of a ventral motor learning task. These models yield insight into the mechanisms by which plasticity in the spinal cord occur, and demonstrate that protein kinase activity is an essential step in mediating long-term neural modifications. In this final section, we will consider the therapeutic potential in altering protein kinase activity for spinal cord injury and related CNS disorders.

Within the wave of secondary processes following spinal cord injury, high levels of glutamate release can have a devastating effect on cell survival (Crowe et al., 1997; McAdoo et al., 1999; Ferguson et al., 2008b). As mGluR activation leads to PLC-mediated release of intracellular calcium stores, PKC activity increases, and in turn ionotropic glutamate receptors can be further potentiated. While this pathway can induce long-term spinal plasticity, the neural microenvironment around the spinal lesion is more vulnerable to excitotoxicity, and this cascade can ultimately lead to cellular degradation and excitotoxic cell death (Choi, 1992; Gereau & Heinemann, 1998; Mills et al., 2001). This has lead researchers to investigate the effect of PKC inhibition on cell survival after injury. Hara et al. showed that following ischemic injury, treatment with the PKC inhibitor staurosporine produced a neuroprotective effect (Hara et al. 1990). This group later showed that the broad protein kinase inhibitor fasudil was also effective in improving locomotor function and tissue sparing following a spinal cord injury (Hara et al., 2000).

As secondary injury processes develop, a glial scar formed by chondroitin sulfate proteoglycans (CSPGs) is created to protect the damaged tissue (Fawcett & Asher, 1999). This scar formation, along with myelin-associated proteins, exerts inhibitory effects on axonal regeneration (McKerracher et al. 1994; Chen et al. 2000). Interestingly, PKC has been shown to be a key signaling mediator that is activated by these inhibitory agents (Sivanskaran et al., 2004). Sivasankaran and colleagues used immobilized substrates coated in either inhibitory myelin proteins or CSPGs to assay neurite outgrowth. They tested a range of PKC inhibitors, and found that inhibiting PKC activity stimulated neurite outgrowth on both the inhibitory myelin protein and CSPG substrates. Further, they were able to confirm these *in vitro* findings in an *in vivo* model of spinal cord injury. Rat subjects were given a dorsal hemisection, followed by an osmotic infusion of the PKC inhibitor Go6976 over the next 14 days. Results showed axonal regeneration in the dorsal column, with fibers crossing the lesion gap and extending as far as 6 mm (Sivasankaran et al., 2004). While this treatment appears promising, they showed very little axonal regeneration of the the corticospinal tract (CST), which is thought to be necessary in order to maximize functional recovery of descending motor control in primates, including humans (Blesch & Tuszynski, 2009). Further work will be needed to determine whether the regeneration promoted by PKC inhibition results in functional connectivity and improved behavioral outcomes.

Recently, many spinal cord researchers have begun focusing on the signaling pathways that are activated by the inhibitory myelin proteins. Interestingly, many of these inhibitory proteins act through their receptors to activate a small GTPase called Rho (Niederost et al. 2002). Rho is known to be important for regulating cytoskeletal structure and guiding axons in the developing CNS, and thus has been become a target of interest for those that seek to

promote the regeneration of axons across spinal cord lesions after injury (Hall, 1998; Dubreuil et al., 2003). Many researchers have focused on inhibiting or altering Rho function after spinal cord injury, and have shown this treatment to be effective in blocking the growth inhibitory factors that are rampant after spinal cord injury (McKerracher et al. 2006; Fehlings et al., 2011). Others have looked further downstream, to the protein kinase that is activated by Rho. Rho-associated protein kinase (ROCK) has been shown to mediate the retraction of neurites *in vitro*, and experimental activation of ROCK is known to regulate myelin phosphotase, an essential component of axonal sprouting (Hirose et al., 1998; Kimura et al. 1996). Thus, ROCK has become an attractive therapeutic target, as specific ROCK inhibition is believed to mitigate the inhibitory effects of those myelin-derived proteins that undermine axonal regeneration. In 2000, Bito and colleagues used cultured, immature cerebellar granule neurons to directly study the effects of ROCK inhibition on neurite outgrowth. By co-transfecting these cells with green fluorescent protein (GFP) and an active form of Rho (V14Rho), they observed a marked retardation of axonal growth. When they then introduced the ROCK inhibitor Y-27632, they found that inhibiting ROCK attenuated the stunted growth, and produced significant axon genesis.

Building on these findings, Dergham and colleagues (2002) tested this same ROCK inhibitor on a variety of substrates coated with myelin inhibitory proteins or CSPG. They too found that *in vitro* administration of Y-27632 promoted the growth of primary neurons across these substrates. Further, they extended these findings to an *in vivo* spinal cord injury model. They gave mouse subjects dorsal hemisections, followed by spinal injection of Y-27632. They found that this ROCK inhibitor not only attenuated axonal dieback, but promoted the regeneration of neurons within the corticospinal tract, generating sprouting that stretched 2-3 mms across the lesion site. The ROCK-inhibited subjects also exhibited a long-term improvement in locomotor function. In 2003, Fournier published a study that extended these findings to rats, showing similar results (Fournier et al., 2003). They found that ROCK inhibition with Y-27632 was not only sufficient to promote neurite outgrowth *in vitro*, but as with the Dergham study, they showed that ROCK inhibition after hemisection could promote CST axons to regenerate across the lesion, as well as produce significant behavioral improvement in comparision to vehicle-treated subjects.

Taken together as a group, these data indicate a strong role for PKC as well as Rho kinases in morphological regeneration of the CST that is thought to be necessary for recovery of function after spinal cord injury (Blesch & Tuszynski, 2009; Nielson et al., 2010). However, recent findings have revealed that, even in the absence of CST regeneration through a spinal cord lesion, there may be substantial sprouting of surviving CST fibers below the lesion site in primates, which has been linked to improved recovery of function in forelimb control (Rosenzweig et al., 2010). This suggests a role for local spinal plasticity in restoring recovery of function in CST-dependent function. The role of mGluRs and PKC flux in these effects is largely unknown, and may represent a fruitful area for further study.

5. Conclusions

This chapter has reviewed the role of mGluRs and down-stream PKC activity as a major factor in a number of forms of plasticity throughout the spinal cord. Its ubiquity indicates a potential common mechanism for a host of complex processes, in both the intact and injured spinal cord. As a critical link between mGluR activation and ionotropic GluR trafficking and

phosphorylation, PKC activity can mediate either the potentiation or depression of synaptic strength, the promotion of neural regeneration or the exacerbation of excitotoxicity. In the future, targeting PKC activity within the appropriate circumstances, and at the right time, will be essential to tailoring effective treatments for both central and peripheral injuries, as well as in the promotion of use-dependent spinal plasticity.

6. Acknowledgements

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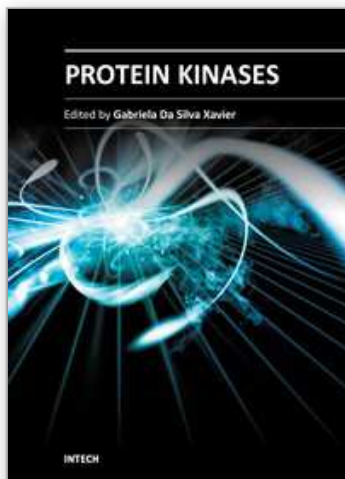
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Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.

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