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Significance of protein kinase C in the neuropsychotoxicity induced by methamphetamine-like psychostimulants

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ABSTRACT

The abuse of methamphetamine (MA), an amphetamine (AMPH)-type stimulant, has been demonstrated to be associated with various neuropsychotoxicity, including memory impairment, psychiatric morbidity, and dopaminergic toxicity. Compelling evidence from preclinical studies has indicated that protein kinase C (PKC), a large family of serine/threonine protein kinases, plays an important role in MA-induced neuropsychotoxicity. PKC-mediated N-terminal phosphorylation of dopamine transporter has been identified as one of the prerequisites for MA-induced synaptic dopamine release. Consistently, it has been shown that PKC is involved in MA (or AMPH)-induced memory impairment and mania-like behaviors as well as MA drug dependence. Direct or indirect regulation of factors related to neuronal plasticity seemed to be critical for these actions of PKC. In addition, PKC-mediated mitochondrial dysfunction, oxidative stress or impaired antioxidant defense system has been suggested to play a role in psychiatric and cognitive disturbance induced by MA (or AMPH). In MA-induced dopaminergic toxicity, particularly PKCδ has been shown to trigger oxidative stress, mitochondrial dysfunction, pro-apoptotic changes, and neuroinflammation. Importantly, PKCδ may be a key mediator in the positive feedback loop composed of these detrimental events to potentiate MA-induced dopaminergic toxicity. This review outlines the role of PKC and its individual isozymes in MA-induced neuropsychotoxicity. Better understanding on the molecular mechanism of PKCs might provide a great insight for the development of potential therapeutic or preventive candidates for MA (or AMPH)-associated neuropsychotoxicity.

1. Introduction

Methamphetamine (MA) is an amphetamine-type dopaminergic stimulant with a high abusive potential. The growth of MA drug abuse has been particularly strong during the last decade (United Nations Office on Drugs and Crime, 2017), and thus MA drug abuse is a current global health problem. MA is similar in chemical structure to dopamine (DA), and taken up by dopaminergic neurons as a substrate for dopamine transporter (DAT). At high concentration, MA can enter dopaminergic neurons by slow diffusion due to its high lipid solubility (Saha et al., 2014). In dopaminergic neurons, MA produces DAT-mediated DA efflux and thus increases the synaptic level of DA (Panenka et al., 2013; Sulzer et al., 2005), which apparently account for the acute effects and the abusive potential of MA (Cruickshank and Dyer, 2009; Darke et al., 2008).

It has been demonstrated that long-term MA drug abuse is associated with neurotoxicity (Moszczynska et al., 2004; Wilson et al., 1996) and psychiatric conditions, such as cognitive impairments (Newton et al., 2004; Rendell et al., 2009) and psychosis/mania (Sato, 1992; Yui et al., 2000). Because clinical studies have shown that chronic MA drug abuse can induce persistent dopaminergic neurotoxicity, especially in nigrostriatal pathway, even after long-term

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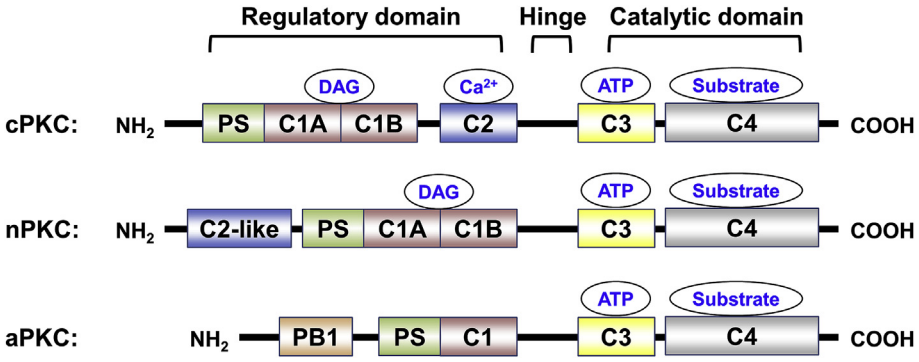

Fig. 1. Schematic representation of the structure and classification of PKC isozymes. PKC isozymes contain a highly conserved C-terminal catalytic domain and a variable N-terminal regulatory domain tethered by a hinge region (Mellor and Parker, 1998; Steinberg, 2008). The C1 domain has cysteine-rich motifs that form the DAG-binding site. The C2 domain contains Ca^{2+}-binding site. PS = pseudosubstrate region. PB1 = Phox and Bem1 domain.

abstinence (McCann et al., 1998; Volkow et al., 2001b), and that the incidence of Parkinson's disease (PD) is greater in MA abusers than in non-drug abuser (Callaghan et al., 2010, 2012), MA drug abuse has been suggested as a potential risk factor of PD. In addition, due to the similarities in symptoms (Sato, 1992; Yui et al., 2000) and longitudinal profiles (Ujike, 2002; Ujike and Sato, 2004), the relevance of MA-induced psychosis/manic episode to schizophrenia has been suggested.

Protein kinase C (PKC) is a large family of serine/threonine kinases that are involved in diverse physiologic and pathologic responses. PKC consists of a C-terminal catalytic domain and an N-terminal regulatory domain connected by a flexible hinge region (Mellor and Parker, 1998; Steinberg, 2008) (Fig. 1). The structure of catalytic domain is highly conserved across PKC isozymes, whereas that of regulatory domain varies among PKC isozymes. PKC is further subdivided into three distinct subfamilies (*i.e.*, conventional, novel, and atypical PKC) based on the structure and regulatory mechanism. The conventional subfamily of PKC isozymes (cPKC: PKCα, PKCβI, PKCβII, and PKCγ) requires both diacylglycerol (DAG) and Ca^{2+} for activation, but the novel subfamily of PKC isozymes (nPKC: PKCδ, PKCε, PKCη, and PKCθ) does not require Ca^{2+}. Neither DAG nor Ca^{2+} is required for the activation of the atypical subfamily of PKC isozymes (aPKC; PKCι/λ, and PKCζ) (Mellor and Parker, 1998). Although the involvement of PKC has been suggested in a wide range of cellular processes, the role of each PKC isozyme in MA-induced neuropsychotoxicity remains elusive. In this review, we summarize the major findings from reports on PKCs in MA neuropsychotoxicity. More importantly, we highlight the role and suggested mechanism of PKC in the DA release, dependence, memory impairment, manic syndrome, and dopaminergic neurotoxicity induced by MA.

1.1. Role of PKC in dopamine release induced by MA or amphetamine (AMPH)

MA is a substrate for the DAT, and increases synaptic DA concentration through the inhibition of DA uptake as well as the induction of DA efflux (reverse transport) via the DAT (Kazahaya et al., 1989; Stephans and Yamamoto, 1995; Yamada et al., 1988). MA-induced synaptic DA release plays a pivotal role in its neuropsychotoxicity (Hamamura et al., 1991; Lin et al., 2007; O'Dell et al., 1993).

It has long been recognized that there is a so-called "PKC domain" at the N-terminus of the DAT structure in which several serine residues can be phosphorylated by PKC (Foster et al., 2002; Lin et al., 2003). PKC activator phorbol 12-myristate 13-acetate (PMA) has been shown to increase the basal phosphorylation level of DAT, resulting in a decrease in DA uptake in DAT-expressing cell system or *ex vivo* synaptosomal preparation in rat (Granas et al., 2003; Huff et al., 1997; Karam et al., 2017; Vaughan et al., 1997). Similarly, it has been reported that MA or its prototype drug amphetamine (AMPH) phosphorylated the N-terminus of DAT (Cervinski et al., 2005; Karam et al., 2017), suggesting that MA-induced DAT phosphorylation is associated with its inhibition of DA uptake *in vitro* and *in vivo*. In addition, AMPH-induced DA efflux was decreased by the N-terminal truncation or the serine to alanine mutation in the N-terminus of DAT (Khoshbouei et al., 2004; Wang et al., 2016). Consistently, pan-PKC inhibitor chelerythrine, Ro31-8220, calphostin C, or NPC15437 has been shown to abolish the reduction of DA uptake and the augmentation of DA efflux induced by MA or AMPH in rat striatum (Kantor and Gnegy, 1998; Sandoval et al., 2001). Specifically, PKCβ inhibitor LY379196 or PKCβ gene knockout decreased AMPH-induced DA efflux in the striatum (Chen et al., 2009; Johnson et al., 2005), suggesting that PKCβ-mediated N-terminal phosphorylation of DAT is important for DA efflux induced by MA or AMPH derivatives. In addition, Cremona et al. (2011) showed that PKC activation triggers DAT internalization in primary dopaminergic neurons or in mouse striatal slices through the phosphorylation of flotilin-1, suggesting that PKC activity is essential for the AMPH-induced DA efflux. These *in vitro* and *ex vivo* findings were supported by *in vivo* microdialysis studies showing that pan-PKC inhibitor chelerythrine or Ro31-8220, or PKCβ-specific inhibitor enzastaurin or ruboxistaurin attenuated extracellular DA release in the nucleus accumbens and associated behavioral changes induced by MA or AMPH (Loweth et al., 2009; Narita et al., 2004; Zestos et al., 2016). It was suggested that PKC-induced DAT phosphorylation facilitates its conformational change favorable for the outward transport of DA in the presence of AMPH (Gnegy, 2003; Kantor and Gnegy, 1998).

In this context, an earlier study has reported that AMPH treatment increases particulate PKC activity in the synaptic plasma membrane fraction prepared from rat striatum (Giambalvo, 1992). Similarly, *in vivo* exposure to 3,4-methylenedioxymethamphetamine, a substituted AMPH, has been shown to induce membrane translocation of PKC in rat cerebral cortex (Kramer et al., 1995). In addition, it has been reported that incubation with AMPH induces PKC activity by increasing intracellular Ca^{2+}, phospholipase C activity, and consequent DAG production in rat striatal synaptosomes (Giambalvo, 2004). Thus, it could be proposed that MA induces PKC-mediated DAT phosphorylation in the plasma membrane via stimulating membrane translocation of PKC or increasing PKC activity via Ca^{2+}/DAG second messenger system, although it has not yet been clarified. Moreover, the activation of trace amine associated receptor 1 (TAAR1) or σ2 receptor has been shown to enhance DA efflux induced by MA or AMPH via PKC (Derbez et al., 2002; Xie and Miller, 2007), suggesting that PKC activation is important for the induction and regulation of DA efflux.

1.2. Role of PKC in the drug dependence induced by MA or AMPH

Systemic or intra-accumbal administration of a pan-PKC inhibitor chelerythrine or NPC15437 has been shown to attenuate conditioned place preference (CPP) and behavioral sensitization induced by MA or AMPH in rodents (Aujla and Beninger, 2003; Narita et al., 2004, 2005; Shibasaki et al., 2011). Moriguchi et al. (2002) have shown that PKC activation enhances N-methyl-D-aspartate (NMDA) receptor-mediated excitatory post-synaptic potential in the neostriatum during withdrawal after repeated MA treatment, possibly, through the phosphorylation of NMDA receptors. In addition, it has been reported that PKCγ

phosphorylation is accompanied by the enhanced histone H3 acetylation of gene promoter regions associated with synaptic plasticity in the limbic brain of mice showing place preference for MA (Shibasaki et al., 2011). In their study, the intracerebroventricular (i.c.v.) administration of chelerythrine, a pan-PKC inhibitor, attenuated, whereas phorbol 12,13-dibutyrate, a pan-PKC activator, potentiated MA-induced place preference. Thus, it is plausible that PKC contributes to the development of MA drug dependence by promoting neural and synaptic plasticity in the relevant brain area.

In contrast, MA exposure activated astrocytes in pure astroglial culture and neuroglia co-culture, and the phosphorylated PKC was localized in activated astrocytes, suggesting that PKC-mediated astroglial activation plays a role in the reward effect of MA (Miyatake et al., 2005; Narita et al., 2005). Furthermore, PKC inhibitor chelerythrine or NPC15437 attenuated MA-induced CPP and behavioral sensitization, and accompanying astroglial activation in the cingulate cortex and nucleus accumbens (Narita et al., 2004, 2005), suggesting that PKC might mediate rewarding effect via the enhancement of neuronal excitation by astroglia-neuron communication in response to MA.

A few studies have identified which PKC subtypes are involved in the development of MA drug dependence, though the results have been inconsistent. Shibasaki et al. (2011) suggested the importance of PKCγ in MA-induced CPP, whereas Liao et al. (2016) reported that systemic injection of rottlerin, a PKCδ inhibitor, attenuates MA-induced CPP in rats. In addition, it has been shown that AMPH-induced behavioral sensitization was attenuated by intra-accumbal infusion of the inhibitor of protein kinase Mζ (PKMζ), an alternative transcript of PKCζ (Song et al., 2013). The precise role of each PKC subtype will be elucidated when evidence is accumulated in future studies. In addition, the involvement of PKC has been studied only in the CPP paradigm and behavioral sensitization induced by MA, thus it needs to be further studied in other experimental models of drug dependence, such as self-administration paradigm. The main findings on the role of PKC in MA-induced drug dependence are summarized in Table 1.

1.3. Role of PKC in memory impairments induced by MA

It has been consistently demonstrated that long-term MA drug abuse is associated with the impairments in attention, working memory, executive function, episodic memory (Newton et al., 2004; Rendell et al., 2009; Simon et al., 2000, 2002, 2004; Thompson et al., 2004), and accompanied by prefrontal cortical and hippocampal dysfunction (Ernst et al., 2000; Paulus et al., 2002; Thompson et al., 2004). Similarly, repeated MA treatment has been shown to induce impairments in recognition memory (Gonzalez et al., 2014; Kamei et al., 2006; Noda et al., 2010; North et al., 2013), spatial memory (Braren et al., 2014; Nagai et al., 2007), and associative memory (Beirami et al., 2018) in rodents, even 4–5 weeks after withdrawal from MA (Kamei et al., 2006; North et al., 2013). In these conditions, failure of task-dependent phosphorylation of extracellular signal-related kinase (ERK) has been found in the prefrontal cortex and hippocampus (Gonzalez et al., 2014; Kamei et al., 2006; Nagai et al., 2007; Noda et al., 2010).

We also reported that repeated MA administration (1 mg/kg/day for 7 days) impairs novel object recognition memory and decrease in ERK phosphorylation in the prefrontal cortex of mice (Mai et al., 2018a, 2018b; Tran et al., 2018), and that this memory impairment lasts, at least, for 28 days after the MA withdrawal (Tran et al., 2018). These changes were accompanied by the phosphorylation of PKCδ in the prefrontal cortex (Mai et al., 2018a, 2018b; Tran et al., 2018), and were attenuated by PKCδ gene knockout in mice (Mai et al., 2018a; Tran et al., 2018). In addition, PKCδ gene knockout facilitated Nrf2 nuclear translocation, glutamate-cysteine ligase (GCL) mRNA expression, and glutathione homeostasis in the prefrontal cortex (Mai et al., 2018a; Tran et al., 2018). Consistently, glutathione peroxidase-1 (GPx-1) expression was enhanced in PKCδ gene knockout mice (Tran et al., 2018), suggesting that PKCδ mediates MA-induced memory impairment

Table 1
Summary of preclinical studies on the role of PKC in drug dependence induced by MA or AMPH.

Subject	MA (or AMPH) treatment	Behavioral paradigm	Main findings relevant to PKC	References
Rat	Prior to CPP: MA (2.0 mg/kg/day, i.p. × 5) During CPP: MA (0.5 mg/kg, i.p. × 2)	CPP	Intra-accumbal infusion of chelerythrine attenuated MA-induced CPP. Phosphorylation of cPKC was induced in the limbic forebrain.	Narita et al. (2004)
Mouse	MA (2.0 mg/kg, s.c. × 5, every 96 h)	Behavioral sensitization	NPC15437 attenuated MA-induced behavioral sensitization and accompanying astroglial activation in the cingulate cortex and nucleus accumbens.	Narita et al. (2005)
Mouse	MA (1.0 mg/kg, s.c. × 3)	CPP	MA-induced CPP was accompanied by the increase in PKCγ phosphorylation in the limbic forebrain. Chelerythrine attenuated MA-induced CPP Phorbol 12,13-dibutyrate potentiated MA-induced CPP	Shibasaki et al. (2011)
Mouse	MA (1.0 mg/kg, i.p. × 3)	CPP	Rottlerin attenuated the establishment and maintenance of MA-induced CPP. Rottlerin also attenuated MA-primed reinstatement of the extinguished MA CPP.	Liao et al. (2016)
Rat	Intra-accumbal infusion of AMPH (20.0 μg/0.5 μl/side, bilateral)	CPP	Intra-accumbal infusion of NPC15437 attenuated AMPH-induced CPP.	Aujla and Beninger (2003)
Rat	AMPH (1.0 mg/kg, i.p. × 4, 2–3 days apart)	Behavioral sensitization	Intra-accumbal infusion of zeta-inhibitory peptide attenuated AMPH-induced behavioral sensitization.	Song et al. (2013)

CPP = Conditioned place preference. Chelerythrine or NPC15437: a pan-PKC inhibitor. Phorbol 12,13-dibutyrate: a pan-PKC activator. Rottlerin: a PKCδ inhibitor. Zeta-inhibitory peptide: a PKMζ inhibitor.

through the down-regulation of glutathione-related enzymatic antioxidant defense system.

Braren et al. (2014) demonstrated that repeated binge dose of MA (30 mg/kg × 2, at 1 week interval) induces spatial working memory impairment in mice 5 weeks after the final MA injection. In their study, MA-induced memory impairment was accompanied by decreases in the expression of PKMζ and dopaminergic D1 receptor, and increase in the expression of glutamatergic receptor GluN2B subunit in the hippocampus, which might be associated with long-term potentiation (LTP). In addition, their follow-up study (Avila et al., 2018) showed that voluntary oral MA administration for 28 days (at average of 5.23 mg/kg/day) impairs spatial learning and spatial working memory even after the withdrawal from MA. Decreases in PKMζ and synaptic plasticity markers, such as postsynaptic density protein-95 and glutamatergic receptor GluA2 subunit, were also observed in the hippocampus (Avila et al., 2018). Thus, the down-regulation of PKMζ may be involved in MA-induced impairments in spatial learning and working memory through the deregulation of hippocampal synaptic plasticity. Combined, the specific role of each PKC subtype in the MA-induced memory impairments might be diverse depending on the dosing regimen, withdrawal period, type of memory, and brain regions, although it needs to be further explored. The main findings on the role of PKC in memory impairments induced by MA or AMPH are summarized in Table 2.

1.4. Role of PKC in mania-like behaviors induced by MA or AMPH

Acute AMPH administration has long been used as an animal model of mania with a good predictive validity (Cosgrove et al., 2016; Young et al., 2011). Similarly, it has been shown that mood stabilizers, including lithium, valproate, or carbamazepine, attenuated the hyperactivity and related neuronal changes induced by acute MA treatment (da-Rosa et al., 2012; Feier et al., 2013; Lee et al., 2000; Lee et al., 1999; Shilling et al., 2006), suggesting that MA administration is also a useful animal model of mania.

In bipolar-manic patients, the enhanced PKC activity has been observed in platelets (Friedman et al., 1993; Hahn et al., 2005) or in postmortem brains (Wang and Friedman, 1996). In addition, lithium and valproate have shown to exert its effect through, as least in part, the inhibition of PKC (Friedman et al., 1993; Hahn et al., 2005; Soares et al., 2000). Therefore, precise mechanism associated with PKC inhibition of lithium, valproate, or tamoxifen has been investigated in AMPH-treated rodent model of mania. Although tamoxifen is a well-known selective estrogen receptor modulator (SERM), tamoxifen and its metabolites have been demonstrated to inhibit PKC activity with a high potency (Ali et al., 2010; O'Brian et al., 1988; Su et al., 1985). In addition, it was suggested that PKC inhibitory activity rather than SERM activity is important for tamoxifen-mediated anti-manic effects (Pereira et al., 2011).

Consistent with results from clinical studies, it has been reported that AMPH-induced hyperactivity was accompanied by increases in the activity and phosphorylation of PKC in the prefrontal cortex, hippocampus, amygdala, or striatum of rodents (Cechinel-Recco et al., 2012; Szabo et al., 2009). PKC activation was followed by an increase in the phosphorylation of PKC substrates, such as myristoylated alanine-rich C kinase substrate, neurogranin and growth-associated protein of 43 kDa (Einat et al., 2007; Szabo et al., 2009). In these studies, lithium attenuated PKC-mediated phosphorylation of glutamatergic receptor GluA1 subunit, which is important in the expression of long-term potentiation, in the prefrontal cortex of AMPH-treated mice (Szabo et al., 2009). In addition, lithium and tamoxifen suppressed AMPH-induced PKC phosphorylation, and subsequent decreases in the expression of nerve growth factor, brain-derived neurotrophic factor and phospho-CREB in multiple brain regions of rats (Cechinel-Recco et al., 2012), suggesting that PKC plays a role in the alteration of neuronal plasticity induced by AMPH.

Table 2
Summary of preclinical studies on the role of PKC in memory impairments induced by MA.

Subject	MA treatment	Memory test	Main findings relevant to PKC	References
Mouse	1.0 mg/kg/day, s.c. × 7	Novel object recognition test	MA-induced visual recognition memory impairment was accompanied by increases in the expression and phosphorylation of PKCδ. PKCδ gene knockout attenuated MA-induced memory impairment in mice via maintaining glutathione-related antioxidant defense system.	Mai et al. (2018a); Mai et al. (2018b); Tran et al. (2018)
Mouse	30 mg/kg, i.p. × 2, 7 days apart	Radial arm maze	MA-induced spatial working memory impairment was accompanied by decrease in PKMζ expression in the hippocampus. Down-regulation of PKMζ expression was associated with the deregulation of LTP-related factors, including glutamatergic receptor GluN2B subunit, in the hippocampus.	Braren et al. (2014)
Mouse	Voluntary oral administration for 28 days (average consumption = 5.23 mg/kg/day)	Radial arm maze	MA-induced spatial reference- and working memory-impairments was accompanied by decrease in the expression of PKMζ and synaptic plasticity markers, including glutamatergic receptor GluA2 subunit and PSD-95 in the hippocampus.	Avila et al. (2018)

LTP = Long-term potentiation. PSD-95 = Postsynaptic density protein-95.

Previous reports indicated that the enzyme activity of mitochondrial complexes and Krebs cycle is reduced in the prefrontal cortex, hippocampus, striatum, and amygdala of AMPH-induced mania model (Moretti et al., 2011; Valvassori et al., 2014). It was also reported that hyperactivity and risk-taking behaviors induced by AMPH are accompanied by increase in the level of oxidative stress markers (Steckert et al., 2012). These changes were consistent with results from post-mortem prefrontal cortex obtained from bipolar disorder patients (Andreazza et al., 2010, 2013). AMPH-induced changes in mitochondrial function and oxidative parameters were attenuated by a PKC inhibitor tamoxifen, suggesting that PKC activation mediates mania-like behaviors through the mitochondrial dysfunction and subsequent oxidative stress in AMPH-induced mania model.

Up to now, little is known about the role of PKC subtypes in AMPH- or MA-induced animal model of mania, but Horiuchi et al. (2013) have shown that PKCε inhibition attenuates MA-induced mania-like behaviors, including hyperlocomotor activity and impaired prepulse inhibition in mice. Clinical studies have suggested that low DAT availability is associated with neuropathology of bipolar disorder (Amsterdam and Newberg, 2007; Anand et al., 2011). In addition, DAT gene knockout or DAT-selective inhibitor has been applied to establish the animal model of mania in rodents (van Enkhuizen et al., 2015). As mentioned above, several PKC isozymes have been implicated with the DAT inhibition and subsequent DA release induced by MA or AMPH (Chen et al., 2009; Cremona et al., 2011; Johnson et al., 2005; Sandoval et al., 2001; Zestos et al., 2016). Thus, it may be possible that other PKC isozymes in addition to PKCε are important for MA- or AMPH-induced mania-like behaviors, although it remains to be explored. The main findings on the role of PKC in AMPH- or MA-induced mania-like behaviors are summarized in Table 3.

1.5. Role of PKC in MA-induced dopaminergic toxicity

Positron emission tomographic studies and post-mortem analyses have shown that long-term MA drug abuse is associated with dopaminergic terminal degeneration in the striatum (McCann et al., 1998; Volkow et al., 2001a, 2001b; Wilson et al., 1996). Similar to clinical finding, MA administration has shown to induce persistent reduction in DA levels and tyrosine hydroxylase (TH) or DAT expression in preclinical animal studies (Hirata et al., 1996; Hirata and Cadet, 1997; Kim et al., 1999; Krasnova et al., 2010; McConnell et al., 2015; O'Callaghan and Miller, 1994). Importantly, it has been reported that binge doses of MA induced nigral neuronal loss in rodents (Ares-Santos et al., 2014; Granado et al., 2011; Sonsalla et al., 1996). In addition, α-synuclein-positive cytoplasmic inclusion bodies were observed in nigral dopaminergic cell bodies after the MA administration (Fornai et al., 2005). Combined with epidemiologic studies showing an increased incidence of PD among MA abusers (Callaghan et al., 2010, 2012), *in vivo* and *in vitro* MA treatment has been suggested as an experimental model relevant to PD (Shin et al., 2017).

Accumulating evidence has suggested that MA neurotoxicity contains oxidative stress, neuroinflammation, mitochondrial dysfunction, and pro-apoptotic changes (Cadet et al., 1994; Dang et al., 2016; Deng and Cadet, 2000; Deng et al., 2001; Jayanthi et al., 2004; McConnell et al., 2015; Nam et al., 2015; Nguyen et al., 2015; Shin et al., 2014). The role of PKCδ among PKC isozymes has been comprehensively studied in these neuropathological processes. Earlier study showed that a PKC inhibitor NPC15437 completely blocks MA-induced production of reactive oxygen species (ROS) in synaptosomes prepared from rat striata (Pubill et al., 2005). In particular, we have shown that genetic or pharmacological inhibition of PKCδ attenuates cytosolic and mitochondrial oxidative stress induced by MA or its analog *para*-methoxymethamphetamine (PMMA) *in vitro* and *in vivo* (Nam et al., 2015; Nguyen et al., 2015; Shin et al., 2014, 2016). In our studies, MA-induced oxidative stress and impaired homeostasis of the glutathione and enzymatic antioxidant system were more pronounced in the

Table 3
Summary of preclinical studies on the role of PKC in mania-like behaviors induced by AMPH or MA.

Subject	AMPH or MA treatment	Behavioral paradigm	Main findings relevant to PKC	References
Rat	AMPH (0.5 mg/kg, i.p., once) or AMPH (0.5 mg/kg, i.p. × 6, 3–4 days apart)	Locomotor activity and risk-taking behavior	Tamoxifen blocked hyperactivity, risk-taking behavior, and GAP-43 phosphorylation in the striatum induced by acute or repeated treatment with AMPH.	Einat et al. (2007)
Mouse	AMPH (2.5 mg/kg/day, i.p. × 10)	–	AMPH treatment increased membrane translocation and activity of PKC in the prefrontal cortex. AMPH-induced PKC activation phosphorylated important factors regulating synaptic function, such as neurogranin and glutamatergic receptors.	Szabo et al. (2009)
Rat	AMPH (2 mg/kg/day, i.p. × 7 or 14)	Locomotor activity	Tamoxifen attenuated hyperactivity and concomitant disruption of mitochondrial energy metabolism in the prefrontal cortex, striatum, hippocampus, and amygdala induced by AMPH.	Moretti et al. (2011)
Rat	AMPH (2.0 mg/kg, i.p., once)	Locomotor activity	AMPH-induced hyperactivity was accompanied by increase in PKC phosphorylation in the hippocampus, prefrontal cortex, amygdala, and striatum. Pre- or post-treatment with lithium or tamoxifen decreased AMPH-induced hyperactivity and PKC phosphorylation.	Cechinel-Recco et al. (2012)
Rat	AMPH (2 mg/kg/day, i.p. × 7 or 14)	Locomotor activity and risk-taking behavior	Tamoxifen attenuated hyperactivity, risk-taking behavior and accompanying oxidative stress in the prefrontal cortex, striatum, hippocampus, and amygdala induced by AMPH.	Steckert et al. (2012)
Rat	AMPH (2 mg/kg/day, i.p. × 7 or 14)	Locomotor activity	Tamoxifen attenuated decreases in enzyme activities of Krebs cycle induced by AMPH in the frontal cortex, striatum, and hippocampus. AMPH-induced hyperactivity was negatively correlated with the enzyme activities of Krebs cycle.	Valvassori et al. (2014)
Mouse	MA (3 mg/kg/day, i.p. × 14)	Locomotor activity and pre-pulse inhibition	PKCε-translocation inhibitor peptide attenuated hyperactivity and impaired pre-pulse inhibition induced by MA.	Horiuchi et al. (2013)

GAP-43 = Growth-associated protein of 43 kDa.

mitochondrial fraction than cytosolic fraction, which may be related to the phosphorylation of tyrosine 311 (Tyr^{311}) residue and the mitochondrial translocation of cleaved PKCδ. It was demonstrated that PKCδ Tyr^{311} phosphorylation by redox sensitive Src family kinases (SFKs) promotes caspase-3-mediated proteolytic cleavage and subcellular localization, including mitochondrial localization (Gong et al., 2015; Konishi et al., 2001; Steinberg, 2015). Similarly, MA-induced PKCδ Tyr^{311} phosphorylation was reversed by a SFKs inhibitor PP2 in our recent study (Tran et al., 2018). Importantly, inhibition of the mitochondrial translocation of cleaved PKCδ attenuated mitochondrial dysfunction (*i.e.*, collapsed transmembrane potential and intramitochondrial Ca^{2+} accumulation), subsequent mitochondrial oxidative stress, and mitochondria-derived pro-apoptotic changes (*i.e.*, cytochrome *c* release, caspase-3 cleavage, increased expression of pro-apoptotic factors/decreased expression of anti-apoptotic factors, or TUNEL–positive cells) induced by MA or its analog PMMA *in vitro* and *in vivo* (Dang et al., 2016; Nam et al., 2015; Nguyen et al., 2015; Shin et al., 2014, 2016). Additionally, we demonstrated that PKCδ inhibition enhances Nrf2 DNA binding activity, GCL induction, and further restores glutathione homeostasis in the striatum in response to MA neurotoxicity (Dang et al., 2018), suggesting that MA-induced disruption of Nrf2/glutathione system requires PKCδ-mediated oxidative stress.

Interestingly, Bordt and Polster (2014) suggested that hydrogen peroxides derived from superoxide radicals caused by mitochondrial dysfunction as well as NADPH oxidase induction activates pro-inflammatory M1 phenotype microglia. In this regard, we have shown that restoration of mitochondrial function achieved by genetic or pharmacological inhibition of PKCδ attenuates microglial activation (in particular, elevated expression of M1 phenotype markers) in the striatum induced by MA or PMMA (Dang et al., 2016; Shin et al., 2014, 2016). In addition, PKCδ inhibition attenuated the membrane translocation of p47phox as well as NADPH oxidase activity induced by MA (Dang et al., 2018). Importantly, p47phox gene knockout or apocynin, an NADPH oxidase inhibitor, attenuated mitochondrial translocation of cleaved PKCδ, and subsequent mitochondrial dysfunction (Dang et al., 2016, 2018). Therefore, our findings suggest that PKCδ significantly mediates the oxidative stress, mitochondrial dysfunction, neuroinflammation, and pro-apoptosis, and that it is a crucial factor for linking these neuropathological events. The main findings on the role of PKC in MA-induced dopaminergic toxicity are summarized in Table 4.

2. Summary and future perspectives

This review introduces the major findings on the role of PKCs in the neuropsychotoxicity induced by MA. Although earlier studies mainly dealt with MA-induced DA release and drug dependence, recent studies have extended understandings to memory impairment, mania-like behaviors, and dopaminergic toxicity following MA administration. PKCβ out of PKCs has been suggested to mediate synaptic DA release through the N-terminal phosphorylation of DAT in response to MA or AMPH. Because increases in synaptic DA concentration and subsequent activation of dopaminergic receptors are important for drug rewarding and reinforcement, it is presumable that PKC could play a crucial role in MA drug dependence. Indeed, it has been suggested that PKC facilitates the gene expression related to synaptic plasticity, and regulates neuronal excitation through the astrocyte-neuron interaction in association with MA drug dependence. In addition, previous reports have demonstrated that isozymes-specific inhibitor of PKCγ, PKCδ, or PKMζ attenuates CPP or behavioral sensitization induced by MA or AMPH. However, the role of PKC needs to be further clarified in the animal model of self-administration, that more closely resembles human pattern of MA intake. In contrast, chronic use of MA has been shown to cause psychiatric symptoms such as hallucination and delusion, which are similar to the symptoms of paranoid schizophrenia (Srisurapanont et al., 2003). In addition, previous studies demonstrated that repeated MA treatment in rodents is a useful animal model for studying schizophrenia as well as MA psychosis (Kamei et al., 2006; Noda et al., 2010; Tran et al., 2018; Ujike, 2002; Ujike and Sato, 2004). Although it has been reported that PKC is involved in the behavioral sensitization and memory impairment induced by repeated MA treatment, the role of PKC needs to be further elucidated in the sensorimotor gating deficit or sociability deficit in this experimental condition. Our recent studies have shown that PKCδ mediated mitochondrial dysfunction, oxidative stress, pro-apoptotic changes, and neuroinflammation in response to MA. In addition, we have suggested that PKCδ links and amplifies these neuropathologic events in a positive feedback manner. PKCδ has also been suggested to

Table 4
Summary of preclinical studies on the role of PKC in dopaminergic toxicity induced by MA or MA analogs.

Subject	MA treatment	Main findings relevant to PKC	References
Rat striatal synaptosomes	Incubation with MA (2 mM) for 2 h	NPC15437 inhibited MA-induced ROS production.	Pubill et al. (2005)
Mouse	8 mg/kg, i.p. × 4 at 2-h interval	MA induced mitochondrial translocation of PKCδ and cleaved PKCδ in the striatum. Genetic depletion of PKCδ attenuated mitochondrial dysfunction, mitochondrial oxidative stress, microglial activation, pro-apoptotic changes, and subsequent nigrostriatal dopaminergic toxicity induced by MA.	Nguyen et al. (2015); Shin et al. (2014)
DopaminergicSH-SY5Y cells	Incubation with MA (1.5 mM) for 12 h	MA induced mitochondrial translocation of PKCδ and cleaved PKCδ. Treatment with PKCδ antisense oligonucleotide attenuated mitochondrial dysfunction, mitochondrial oxidative stress, mitochondrial loss of homeostasis in glutathione-related antioxidant system, pro-apoptotic changes, and dopaminergic toxicity induced by MA.	Nam et al. (2015)
Mouse	35 mg/kg, i.p. × 1	Apocynin, a NADPH oxidase inhibitor, or p47phox gene knockout inhibited MA-induced mitochondrial translocation of cleaved PKCδ in the striatum.	Dang et al. (2016)
Mouse	PMMA (MA analog), 60 mg/kg, i.p., twice a day for consecutive 4 days	PMMA induced PKCδ phosphorylation and mitochondrial translocation of cleaved PKCδ in the striatum. Genetic depletion of PKCδ attenuated mitochondrial dysfunction, mitochondrial oxidative stress, microglial activation, increases in pro-inflammatory cytokines, pro-apoptotic changes, and subsequent nigrostriatal dopaminergic toxicity.	Shin et al. (2016)
Mouse	35 mg/kg, i.p. × 1	MA induced the expression, phosphorylation, and cleavage of PKCδ in the striatum. Genetic depletion of PKCδ inhibited the phosphorylation and membrane translocation of p47phox, and NADPH oxidase activity induced by MA. Genetic depletion of PKCδ enhanced Nrf2/glutathione antioxidant signaling in response to MA, and inhibited microglial activation, pro-apoptotic changes, and subsequent nigrostriatal dopaminergic toxicity.	Dang et al. (2018)

ROS = Reactive oxygen species. PMMA = *para*-methoxymethamphetamine.

Table 5
Respective roles of each PKC subtype in the neuropsychotoxicity induced by MA-like psychostimulants.

PKC subtype	Neuropsychotoxic changes	Suggested role	References
PKCβ	DA efflux	PKCβ phosphorylates the N-terminal domain of DAT, which is essential for DA efflux induced by MA or AMPH derivatives. Consistently, it was reported that PKCβ-specific inhibitor suppressed extracellular DA release in the nucleus accumbens induced by AMPH.	Chen et al. (2009); Johnson et al. (2005); Zestos et al. (2016)
PKCγ	Dependence	Enhanced PKCγ phosphorylation is involved in the development of MA-induced place preference	Shibasaki et al. (2011)
PKCδ	Dependence	PKCδ plays a role in the development, maintenance, and reinstatement of MA-induced place preference	Liao et al. (2016)
	Visual recognition memory impairments	Enhanced PKCδ phosphorylation mediates MA-induced recognition memory impairments by disrupting glutathione-related antioxidant machinery.	Mai et al. (2018a); Mai et al. (2018b); Tran et al. (2018)
	Dopaminergic toxicity	PKCδ plays a causal role in the MA-induced *in vitro* and *in vivo* dopaminergic toxicity through the facilitation of oxidative stress, mitochondrial dysfunction, apoptotic changes, and neuroinflammation.	Dang et al. (2016); Dang et al. (2018); Nam et al. (2015); Nguyen et al. (2015); Shin et al. (2014)
PKCε	Mania-like behaviors	PKCε is involved in the mania-like behaviors (e.g., hyperactivity and impaired pre-pulse inhibition) induced by MA.	Horiuchi et al. (2013)
PKMζ	Dependence	PKMζ in the nucleus accumbens core is important for the expression of behavioral sensitization induced by AMPH	Song et al. (2013)
	Spatial reference- and working-memory impairments	Decrease in PKMζ expression is linked to the deregulation of LTP- and synaptic plasticity-related factors in the hippocampus, and consequent memory impairments induced by MA.	Avila et al. (2018); Braren et al. (2014)

play a mechanistic role in memory impairments and down-regulation of task-evoked ERK phosphorylation induced by repeated MA treatment in the prefrontal cortex via mediating oxidative stress and impaired homeostasis of glutathione-related antioxidant defense system. On the other hand, it has been suggested that the down-regulation of PKMζ interferes with LTP formation in the hippocampus, and it induces subsequent memory impairment in response to MA. In terms of AMPH- or MA-induced animal model of mania, mood stabilizers, such as lithium and valproate as well as tamoxifen, inhibited mania-like behaviors via PKC inhibition. Importantly, PKC may be important for the regulation of synaptic plasticity and mitochondrial function in multiple brain regions related to animal model of mania. The role of each PKC subtype in the neuropsychotoxicity induced by MA-like psychostimulant is summarized in Table 5. Combined, this review provided major findings for the better understanding on the significant role of PKCs in the neuropsychotoxicity induced by MA or AMPH. However, further studies on the PKC as a potential molecular target for the therapeutic intervention on the neuropsychotoxic disorders induced by psychostimulants (MA and AMPHs) are certainly required.

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