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Antioxidant cascades confer neuroprotection in ethanol, morphine, and methamphetamine preconditioning

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1. Introduction

Abuse of addictive substances is associated with central nervous excitability, cognitive and behavioral impairment, and even irreversible neuronal damage in the central nervous system (CNS) (Parrott, 2018). The mechanisms underlying these processes include cytoplasmic and extracellular ionic imbalance, free radical production, excitotoxicity, inflammation, and apoptotic cell death (Abrahao et al., 2017; Solinski et al., 2014; Yang et al., 2018). However, long-term exposure to a low dose of addictive substances, such as ethanol (EtOH), morphine, and methamphetamine (METH), has been shown to protect the mammalian brain against damage caused by subsequent lethal or toxic stimulation, a phenomenon is known as “preconditioning”. The beneficial effects of preconditioning have been observed in the context of transient ischemia/reperfusion (I/R), hypoxia, hypo-/hyperthermia, ischemic stroke, trauma, and neurodegenerative diseases (Arabian et al., 2018; Peart et al., 2005; Su et al., 2017). Besides, specific preconditioning stimuli protect against a wide range of injuries in various disease models, suggesting a “cross-tolerance” effect.

Most addictive drugs affect normal brain function; as most neurons do not regenerate, this can result in long-lasting or permanent neurological dysfunction. However, substance abusers that have abstained for a relatively long period of time and naïve individuals often experience more severe effects from high-dose or binge-like drug intake than individuals who regularly consume a low or escalating dose. For example, more extensive degeneration of the striatal dopamine (DA) system can occur in a naïve user if their first use of the drug is at a dose comparable to those taken by experienced users (Kramer et al., 1967). In addition, heavy consumption of EtOH is associated with up to a 43% higher incidence of diabetes compared to moderate intake (Ronksley et al., 2011). The preconditioning effect complicates the elucidation of mechanisms underlying substance-elicited effects on the brain.

Antioxidant activity has been suggested to play a critical role in the preconditioning process. In this review, we discuss the mechanisms of EtOH, morphine, and METH preconditioning in terms of redox regulation in the CNS and their clinical relevance.

2. EtOH

EtOH, which is commonly abused in the form of a beverage, has high addiction and neurotoxic potential. Excessive drinking leads to brain shrinkage; deficits in memory, cognition, and motor function; and impaired communication, which are associated with increased risk of stroke and neurodegenerative disorders such as Alzheimer's disease (AD) (Ducroquet et al., 2013; Heymann et al., 2016). The neurotoxic mechanisms of EtOH have been extensively investigated. Heavy chronic or acute EtOH exposure can cause neuronal damage and permanent neuronal loss through increased production of reactive oxygen species (ROS), mitochondrial dysfunction, neuroinflammation, and dysregulation of glutamatergic or dopaminergic pathways (Pereira et al., 2015). EtOH reaches the brain by penetrating the blood–brain barrier and is metabolized through oxidation to acetaldehyde via cytochrome P450-dependent signaling. This process is coupled to ROS generation and perturbation of the cellular redox balance. Excess ROS attack lipids, proteins, and nucleic acids in the cell, leading to neurodegeneration (Hernandez et al., 2016). However, some studies have shown that light to moderate alcohol consumption reduces the risk of stroke (Reynolds et al., 2003) and AD (Stetler et al., 2014; Xu et al., 2017). EtOH preconditioning increases resistance to ischemic damage over two different time periods (Yamaguchi et al., 2002). The early phase of protection is between 2 and 4 h after ingestion, whereas the later phase emerges after 24 h (Yamaguchi et al., 2002). Although the mechanism of the former has not been established, the latter is thought to be triggered by nitric oxide (NO) and adenosine generated during EtOH exposure (Yamaguchi

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et al., 2002). Most studies investigating the effects EtOH preconditioning have used a model of EtOH pretreatment for 24 h, as greater protection is conferred by the later as compared to the early phase (Kamada et al., 2004; Nandagopal et al., 2001). One study found that EtOH preconditioning for 24 h reduced I/R-induced oxidative DNA damage and delayed neuronal degeneration and death in the hippocampus of mice (Wang et al., 2010). In cultured neurons or brain slice cultures, neurodegeneration induced by amyloid-β (Aβ) was mitigated by pretreatment with a moderate concentration of EtOH (Collins et al., 2010; Khodaie et al., 2018); and a regimen consisting of 3 g/kg EtOH injection into rats prior to induction of spontaneous intracerebral hemorrhage delayed hematoma formation in the first 3 h (Cheng et al., 2018). These results demonstrate that alcohol preconditioning protects against subsequent brain injury.

The mechanism of EtOH preconditioning may involve the alleviation of oxidative stress, which occurs when the balance between oxidants and antioxidants is perturbed due to excess levels of ROS or malfunctioning of the cellular antioxidant system (Singh et al., 2019). ROS are free radicals such as superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (·OH) that are generated by enzymes including NADPH oxidase (NOX), xanthine oxidase, and monoamine oxidase in the electron transport chain of mitochondria. An antioxidant system comprising superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) scavenge ROS to maintain redox homeostasis in cells (Angelova and Abramov, 2018). ROS levels were found to be increased in an I/R model (Prieto and Monsalve, 2017), but ischemic preconditioning alleviated oxidative stress and enhanced neuronal survival by increasing the expression of antioxidant factors such as nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), and quinone oxidoreductase 1 and inducing NO production and neuronal NO synthase (NOS) and Mn-SOD activities (Hussein et al., 2016; Scorziello et al., 2007).

Preconditioning with moderate EtOH (20–30 mmoL/L) conferred neuroprotection in rat brain slice cultures by suppressing the increases in $O_2^{\cdot -}$ and arachidonic acid (AA) caused by Aβ or glycoprotein 120 (gp120) (Belmadani et al., 2001). AA is an essential polyunsaturated fatty acid that can cause oxidative stress by stimulating ROS production (Guerra and Otton, 2011; Yuan et al., 2017). In mouse hippocampus, pretreatment with 0.48 g/kg EtOH for 24 h prior to I/R protected the brain against damage induced by 20 min of global ischemia through activation of Ca^{2+}-activated potassium (BK_{Ca}) channels, which inhibited ROS production and thereby prevented neuronal injury (Wang et al., 2010). BK_{Ca} channels are widely distributed in the plasmolemma and mitochondrial membrane and regulate neuronal excitability and Ca^{2+} signaling through negative-feedback (Lee and Cui, 2010). The channels are coupled with protein kinase C (PKC) (Isaacson and Murphy, 2001) via N-methyl-d-aspartate receptor (NMDAR) subunit 1 (NR1) in the brain (Zhang et al., 2018). BK_{Ca} channel opening was shown to reduce NMDAR-mediated Ca^{2+} overload, inhibited ROS generation, and increased neuronal survival following I/R (Kulawiak et al., 2008; Wang et al., 2010). So it is reasonable to postulate that the preconditioning of ethanol during cerebral I/R may be partly through BK_{Ca} dependent-Ca^{2+} influx prevention and ROS reduction pathway. However, in global forebrain ischemia of gerbils models, 0.48 g/kg ethanol preconditioning increases the activity of NOX ($p67^{phox}$) to produce small amount of ROS which results in only slight fluctuations in redox status (Wang et al., 2007). A synthetic dismutator of $O_2^{\cdot -}$ abrogated the protective effects of the BK_{Ca} channel activator NS1619 in a cardiac mitochondrial preconditioning model, indicating that BK_{Ca} channel function depends on ROS (Stowe et al., 2006). It is thus presumed that EtOH preconditioning stimulates NOX activity, resulting in the generation of ROS that then elicit adaptive responses such as BK_{Ca} channel opening, leading to a reduction in ROS levels and preventing acute toxicity and damage to neurons.

EtOH preconditioning exerts neuroprotection by regulating the activity of the NR1 subunit of NMDAR, which is coupled to BK_{Ca} channels; it can also modulate the activity of the NR2 subunit to alleviate NMDAR-mediated excitotoxicity (Mitchell et al., 2016; Stetler et al., 2014). In mixed primary cultures of cerebellar neurons, 30 mmoL/L EtOH preconditioning for 3 days protected against Aβ-induced neurotoxicity and increased phospho-activation of the non-receptor tyrosine kinases Src and proline-rich tyrosine kinase 2, thereby promoting synaptic NMDAR localization via tyrosine 1472 phosphorylation of NR2B subunits and stimulating downstream peroxiredoxin-2 (Prx2) signaling (Mitchell et al., 2016). Prx2 is a neuron-specific Prx isoform that protects neurons against ischemia-induced oxidative stress by directly modulating the redox-sensitive thioredoxin (Trx)-apoptosis signal-regulating kinase 1 (ASK1) signaling complex (Gan et al., 2012). ASK1 is a member of the mitogen-activated protein kinase kinase kinase family whose activity is tightly regulated through phosphorylation and interaction with binding partners such as Trx (Obsil and Obsilova, 2017). Trx-ASK1 signaling mediates cellular responses to oxidative stress including cell proliferation, inflammation, and survival (Mao et al., 2019). NMDAR present in the postsynaptic density (i.e., synaptic NMDAR) and in other areas (i.e., extra-synaptic NMDAR) promotes neuronal survival and death, respectively (Pickard et al., 2000; Rao and Craig, 1997). Synaptic NMDAR activity boosts intrinsic antioxidant defense including Trx activity, reducing the level of over-oxidized Prx and enhancing resistance to oxidative stress (Papadia et al., 2008). Thus, neuroprotection may be associated with the synaptic localization of NMDAR, which enables its activation of antioxidant processes including the Prx system (especially Prx2) (Belmadani et al., 2001, 2003; Collins et al., 2010; Khodaie et al., 2018). This hypothesis was also supported by the observation that in co-cultured cerebellar neurons and glia, pretreatment with a combination of 10 mmoL/L EtOH and 5 μmoL/L trans-resveratrol prevented Aβ-induced neurotoxicity by increasing Prx2 levels, whereas pretreatment with either one alone for 3 days did not have this effect (Khodaie et al., 2018), indicating that synaptic localization of NMDAR is increased by combinatorial preconditioning and induces antioxidant processes. Trans-resveratrol is a phytochemical and polyphenolic compound found in wine; preconditioning with trans-resveratrol (25 μmoL/L) inhibited ROS production by activating Nrf2 in both *in vivo* and *in vitro* cerebral ischemia models (Narayanan et al., 2015). These results suggest that the synergistic effect of EtOH and trans-resveratrol are attributable to their antioxidant properties.

In rat brain slice cultures, preconditioning with a moderate concentration of EtOH (20–30 mmoL/L) initially stimulated synaptic NMDAR, activated heat shock protein 27 (Hsp27) via PKCε and focal adhesion kinase (FAK), and protected against cell death induced by Aβ and gp120 (Collins et al., 2010; Sivaswamy et al., 2010). Mammalian Hsp27 is a molecular chaperone that participates in the correct folding of proteins and helps to maintain their native conformation under conditions of stress (Arya et al., 2007). Hsp27 protects neurons against apoptosis triggered by oxidative stress and increases antioxidant defense by reducing ROS levels (An et al., 2008), thus serving as an intracellular regulator of cellular redox state. PKC inhibition was shown to block FAK activation and prevent the upregulation of Hsp27 induced by moderate EtOH preconditioning; in addition, the NMDAR blocker memantine antagonized FAK activation and mitigated Aβ neurotoxicity (Mitchell et al., 2009). These findings suggest that activation of synaptic NMDAR by EtOH preconditioning leads to the activation of the downstream effectors PKC, FAK, and Hsp27, which could enhance antioxidant capacity and confer neuroprotection.

EtOH preconditioning directly affects the expression of key enzymes involved in redox regulation. In hippocampal HT22 cells, acute administration of a sub-lethal dose of EtOH (17 mmoL/L) stimulated the transcription of multiple factors including SOD1, SOD2, GPX genes (e.g., *GPX1*), glutamate-cysteine ligase catalytic (Gclc) subunit, and Trx reductase (TrxR) genes (e.g., *TrxR1*) belonging to the classical, glutathione/glutaredoxin, and Trx/Prx antioxidant systems. Consistent with these changes, the activities of SOD, GPX, glutathione-S-reductase

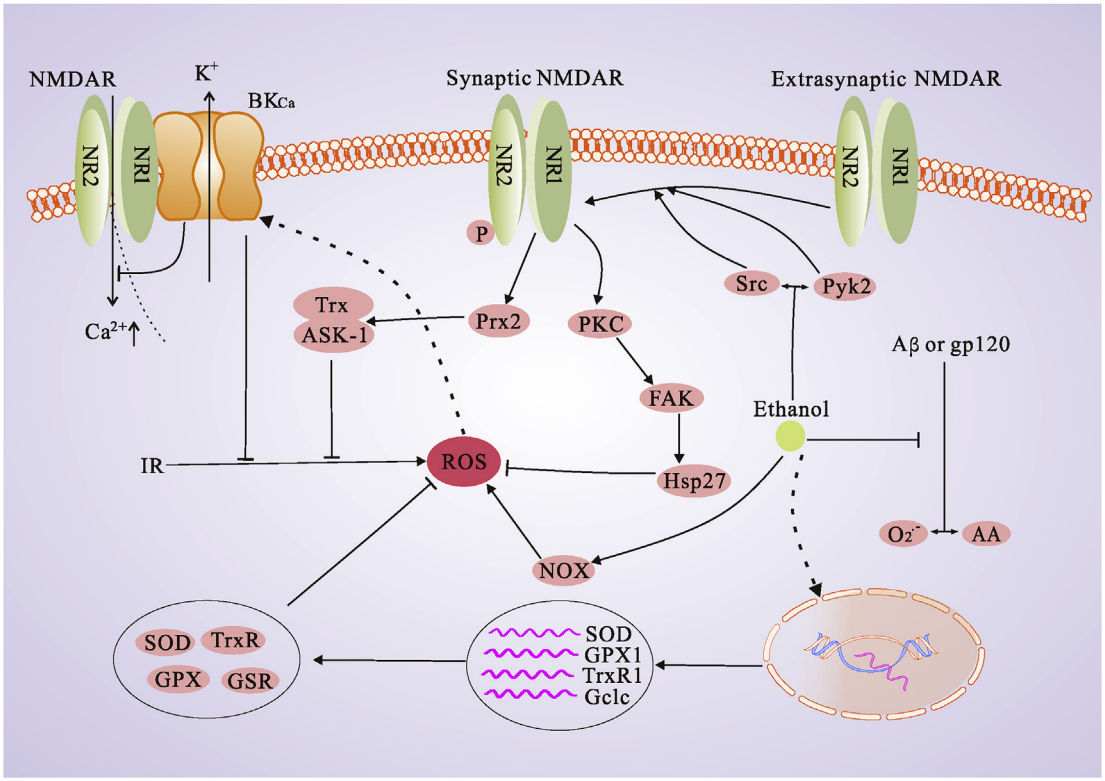

Fig. 1. The redox regulatory pathways in the mechanism of ethanol preconditioning. Ethanol preconditioning inhibits Ca^{2+} overload and ROS by activating BK_{Ca} channel, increases synaptic NMDAR via Src and Pyk2 and then upregulates the level of Prx2 and Hsp27 to inhibit ROS. In addition, ethanol preconditioning facilitates the expression of antioxidant enzymes and the production of proteins such as SOD, GPX, and GSR etc.

(GSR), and TrxR were also increased (Casanas-Sanchez et al., 2016). Notably, *CAT* gene expression was decreased at 24 h whereas CAT activity was increased at 48 h, suggesting the post-translational modulation of CAT, which may be associated with an increase in H_2O_2 level through PKCδ-dependent phosphorylation (Cao et al., 2003; Casanas-Sanchez et al., 2016). The effects of EtOH on SOD activity are controversial, as some studies have reported a decrease (Ledig et al., 1981) or no change (Gonenc et al., 2005) in SOD level in the presence of EtOH. This discrepancy may be due to differences in dosing regimen and duration of EtOH exposure. Additionally, neurons in different subregions of the brain may exhibit distinct responses to EtOH preconditioning depending on myelination, topology, and the number of synaptic connections, which can influence sensitivity to changes in ROS levels; indeed, it was reported that the frontal cortex, substantia nigra, and hippocampus are more sensitive to oxidative stress than other brain regions (Wang and Michaelis, 2010; Wang et al., 2005).

In summary, the protective effects of EtOH preconditioning involve BK_{Ca} channel- and NMDAR-dependent oxidative signaling cascades and transcriptional regulation of antioxidant enzymes and proteins that act in coordination to enhance cellular antioxidant capacity (Fig. 1).

3. Morphine

Morphine is a potent non-selective opioid receptor (ODR) agonist that is commonly used as an analgesic but has high addiction potential. ODR is a G protein-coupled receptor that is broadly expressed and has variable effects in the CNS. Morphine induces apoptosis in neurons (Boronat et al., 2001; Hu et al., 2002; Mao et al., 2002; Wen et al., 2017); neurotoxicity associated with prolonged exposure to morphine is linked to NMDAR signaling and the downregulation of the anti-apoptotic protein B cell lymphoma 2 (Bcl-2) and upregulation of the pro-apoptotic proteins caspase-3 and Bcl-2-associated X protein (Bax) (Mao et al., 2002). However, morphine preconditioning was shown to protect against brain damage under hypoxia/hypoglycemia, ischemia, and Parkinson's disease (PD) models (Ammon-Treiber et al., 2005; Wang et al., 2018; Zhao et al., 2006).

Chronic exposure to 1 μmoL/L morphine prevented staurosporine-induced neuronal apoptosis via downregulation of Bax and Hsp70, whereas naloxone partially blocked morphine-induced decreases in Bax and Hsp70 levels in neurons, demonstrating that the neuroprotective effects of morphine are mediated by ODR (Cui et al., 2008). There are four subtypes of ODR—namely, μODR, δODR, κODR, and nociceptin receptor. The analgesic effect of morphine is attributed to its μODR agonist function (Gross, 2003), which is distinct from its role in ischemic tolerance that involves δODR. δODR agonism does not cause adverse effects upon exposure to opioids, which activate μODR or κODR (Peart et al., 2011). Chronic morphine use was shown to increase expression and facilitate cellular redistribution of δODR in several subregions of the brain (Bie et al., 2010; Ma et al., 2006; van Rijn et al., 2013).

The neuroprotection conferred by morphine preconditioning is abolished by the selective δ_1ODR antagonist 7-benzylidenenaltrexone but is unaffected by antagonists of μODR, κODR, or δ_2ODR (Gwak et al., 2010; Rostami et al., 2012), implying that this effect involves δ_1ODR signaling. δODR activates endogenous protective pathways and maintains intracellular ion homeostasis (Grant Liska et al., 2018); δ_1ODR is coupled to G protein and has various functions including inhibition of adenylate cyclase and voltage-dependent Ca^{2+} channels and activation of phospholipase C and K_{ATP} channels (Barry and Zuo, 2005). The opening of mitochondrial K_{ATP} (mK_{ATP}) channels enhanced cell survival under oxidative stress (Yang et al., 2016) and, in the context of morphine preconditioning, increased CAT activity and decreased malondialdehyde (MDA) level. Preconditioning with addictive doses of morphine (10–30 mg/kg/day) for 5 days reduced oxidative stress in hippocampal neurons 24 h after I/R for 30 min by enhancing antioxidant capacity, as evidenced by the downregulation of MDA and

increase in CAT activity; these effects were abolished by 5-hydroxydecanoate, a selective mK_{ATP} channel blocker (Arabian et al., 2017). MDA, the final product of lipid peroxidation mediated by free radicals, exerts cytotoxic effects by cross-linking proteins and nucleic acids (Tsikas, 2017). The decrease in MDA level resulting from chronic morphine exposure may be due to either decreased ROS production or increased clearance of oxidative metabolites. Moreover, the increase in CAT activity in the hippocampus caused by chronic morphine preconditioning suggests an enhancement of antioxidant capacity. Supporting this possibility, preconditioning with 50 μmoL/L morphine for 24 h alleviated mitochondrial dysfunction and inhibited the generation of intracellular ROS induced by 100 μmoL/L 6-hydroxydopamine (6-OHDA) *in vitro* (Wang et al., 2018). In addition, morphine (50 or 100 μmoL/L) preconditioning for 30 min protected against 6-OHDA-induced neurotoxicity by reversing the increases in intracellular ROS and Ca^{2+} levels and restoring mitochondrial membrane potential in SH-SY5Y cells (Elyasi et al., 2014, 2019). However, conflicting findings have been reported regarding the changes in ROS levels in the preconditioning process. In an *in vitro* study, morphine (3 μmoL/L) preconditioning for 30 min prevented cell death in cerebellar Purkinje cells following 20 min oxygen and glucose deprivation (OGD) and 5 h reperfusion (Lim et al., 2004); this effect was partly abrogated by 5-hydroxydecanoate, or the mitochondrial electron transport inhibitor myxothiazol which can inhibit production of ROS in mitochondria (Turrens, 2003). A positive feedback loop between mK_{ATP} channels and free radicals has been proposed to explain these observations: free radicals activate mKATP channels, leading to the production of more free radical that potentiate neuroprotective processes to counter oxidative stress induced by subsequent lethal or toxic stimulation (Lim et al., 2004). Although the underlying mechanisms remain unclear, these results indicate that activating mK_{ATP} channels and stimulating free radical production are important events in morphine preconditioning.

In mouse primary cortical neurons, morphine (3 μmoL/L) preconditioning for 1 h protected against injuries induced by OGD through downregulation of the microRNA miR-134 (Meng et al., 2016). Meanwhile, miR-134 silencing stimulated ATP production and mitochondrial respiratory enzyme complex activity, decreased MDA and 4-hydroxynonenal levels, and increased SOD activity in the hippocampus of a rat epilepsy model (Sun et al., 2017). These findings indicate that non-coding RNAs are involved in the redox regulation of morphine preconditioning.

Mammalian target of rapamycin (mTOR) controls cellular energy consumption and integrates multiple intra- and extracellular signals to regulate cell death and survival. mTOR signaling also contributes to the protective effects of morphine preconditioning, as evidenced by the fact that the mTOR inhibitor rapamycin reduced SOD level in the hippocampus of rats exposed to morphine (Arabian et al., 2018). Consistent with this finding, SOD activity was shown to be correlated with activation of mTOR/phosphatidylinositol-3-kinase (PI3K)/serine threonine kinase (Akt) signaling (Kennedy and Lamming, 2016). SOD converts $O_2{\cdot}^-$ into H_2O_2 and modulates the PI3K/Akt signaling pathway (Leslie, 2006). Thus, morphine preconditioning protects the brain against ischemic injury via mTOR phosphorylation and activation, which induces antioxidant factors that counter oxidative stress.

Additionally, subcutaneous administration of incremental doses of morphine (10–30 mg/kg/day) for 5 days prior to global brain ischemia protected against I/R-induced oxidative stress and apoptosis in the hippocampus; this effect was abolished by naloxone and the NOS inhibitor N-omega-nitro-l-arginine methyl ester (Arabian et al., 2015), implying that morphine preconditioning functions through a mechanism that depends on δ_1ODR and NO signaling (Fig. 2). Adenosine receptors have also been implicated in morphine-associated renal protection (Habibey and Pazoki-Toroudi, 2008; Pazoki-Toroudi et al., 2010). However, whether there are other mechanisms in the brain besides δ_1ODR signaling that contribute to this process remains to be determined.

4. METH

METH is an illegal, addictive, and frequently abused psychostimulant that has toxic effects including depletion of monoamines, neuronal injury (e.g., apoptosis, necroptosis, and autophagy), and cognitive and behavioral impairment (Sambo et al., 2018; Wen et al., 2019; Xiong et al., 2016, 2017). METH increases DA oxidation, generating a large number of ROS ($O_2{\cdot}^-$, H_2O_2, ·OH) and reactive nitrogen species (NO) that are toxic to neurons (Wen et al., 2016; Yang et al., 2018). There is disagreement over the best way to model repeated METH exposure, with some researchers arguing that escalating doses simulate the conditions of drug abuse and others suggesting that this amounts to METH preconditioning, which protects against damage to the monoaminergic neurotransmitter system (Johnson-Davis et al., 2004; Segal et al., 2003). However, changes in monoamine levels following chronic exposure to sub-toxic doses of METH vary across brain regions (Cadet et al., 2009a, 2011; Graham et al., 2008). For example, preconditioning with an escalating doses of METH (from 0.5 to 14 mg/kg/day) for 3 days followed by METH challenge (six 5 mg/kg doses at 1-h intervals or three 10 mg/kg doses at 2-h intervals) alleviated the depletion of striatal DA but not serotonin (5-HT) in rats; in contrast, METH pretreatment had negligible effects on 5-HT levels in the cortex and hippocampus (Graham et al., 2008). Similarly, cumulative doses of METH (from 0.5 to 14 mg/kg/day) protected against DA depletion caused by METH challenge (six 5 mg/kg doses at 1-h intervals, 1 day after preconditioning) in the striatum and cortex, but did not prevent the depletion of 5-HT in the striatum, although a slight improvement was observed in the cortex (Cadet et al., 2009a). Additionally, escalating doses of METH (five doses of 2.5, 5.0, or 7.5 mg/kg at 6-h intervals) countered DA and 5-HT depletion induced by METH (five doses of 12.5 mg/kg at 4-h intervals) challenge in the rat striatum and cortex, while no significant change was observed in 5-HT level in the hippocampus (Danaceau et al., 2007). In another study, pretreating rats with METH (1.0–10 mg/kg/day) alleviated DA and 5-HT reductions in the striatum and hippocampus following two METH challenges (six 5 mg/kg doses at 1-h intervals) separated by 2 days (Hodges et al., 2011). Thus, the protective effects of METH preconditioning against subsequent METH challenge vary according to brain region and neurotransmitter type. METH concentrations in the plasma and brain during a high-dose METH binge (four doses of 6 mg/kg at 2-h intervals) were unaffected by prior METH exposure (0.1–4.0 mg/kg over 14 days), indicating that pharmacokinetic changes are not the major factors responsible for neuroprotection (O'Neil et al., 2006). Moreover, METH-preconditioned animals had a higher body temperature than controls, indicating that the protective effect is also independent of temperature changes (Graham et al., 2008; Hodges et al., 2011).

METH preconditioning may affect neurons by modulating the redox state so that subsequent binge doses of METH or other insults do not cause the production of ROS at levels that can cause degeneration of DA terminals. In an *in vitro* study, METH (0.5 mmoL/L) preconditioning for 24 h alleviated oxidative stress induced by 6-OHDA in MN9D dopaminergic cells, as evidenced by the fact that the decline in ATP level and nuclear condensation were mitigated (El Ayadi and Zigmond, 2011). In studies investigating transcriptional changes in rat brain induced by a similar METH regimen (Cadet et al., 2009a; Graham et al., 2008), preconditioning followed by administration of high METH doses altered the expression of antioxidant genes (Cadet et al., 2009b, 2011). In the ventral midbrain of rat, METH challenge increased the mRNA expression of Hsp27, brain-derived neurotrophic factor (BDNF), SOD, HO-1, and GPX-1 both without and with METH preconditioning, with especially large changes observed in the latter group (Cadet et al., 2009b). Antioxidant enzymes such as SOD, CAT, and GPX may mediate the effects of METH preconditioning by preventing METH-induced ROS production (Cadet and Brannock, 1998). Hsp27 overexpression increased lifespan and enhanced locomotor performance in *Drosophila melanogaster* treated with the neurotoxin dichlorvos in part by

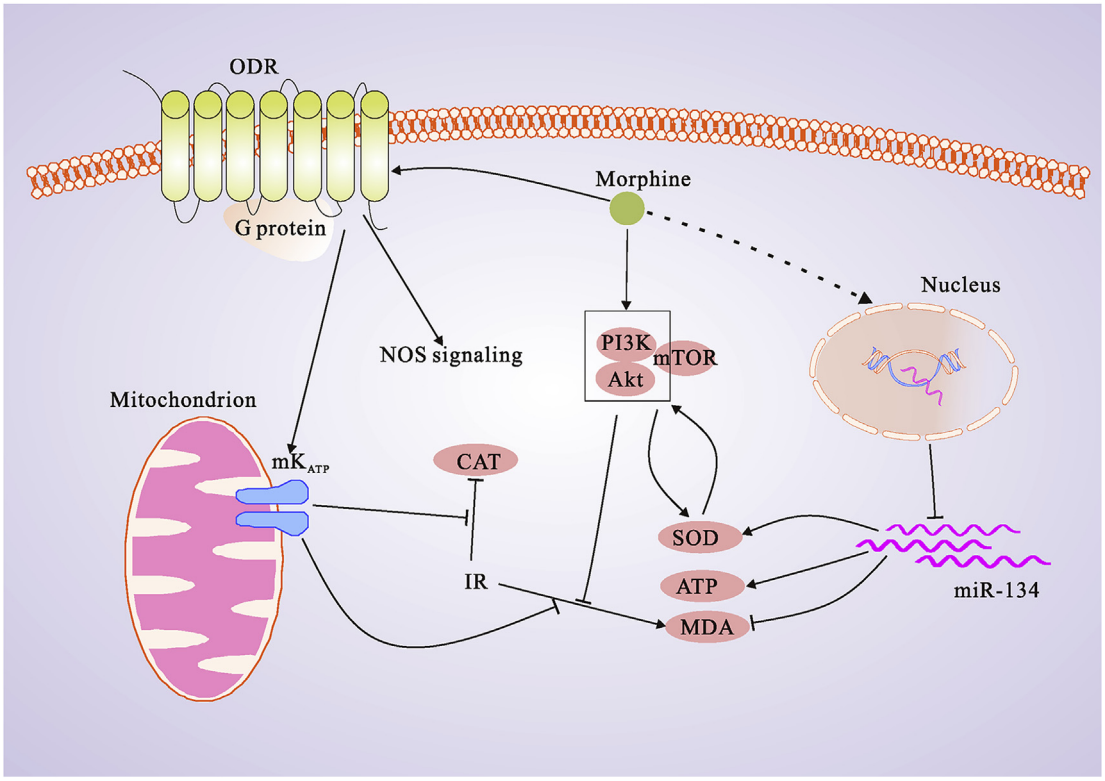

Fig. 2. The anti-oxidative mechanism of morphine preconditioning. Morphine preconditioning can confer protective effects mainly through ODR-dependent mK$_{ATP}$ channel signaling, mTOR pathway, and NOS signaling pathway. Non-coding RNA as miR-134 also serves as a modulator of oxidative stress in preconditioning effects of morphine.

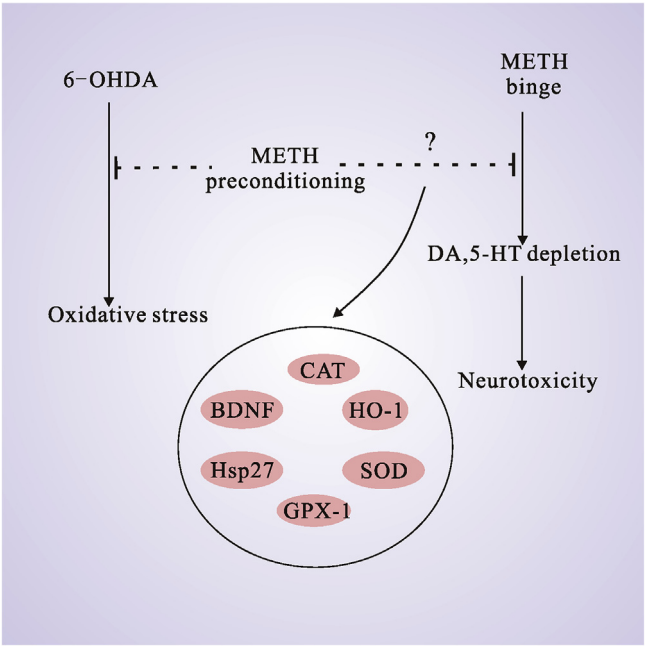

Fig. 3. Factors associated with oxidative stress in METH-induced preconditioning. METH preconditioning can protect against the DA and 5-HT depletion in distinct brain areas of METH-induced neurotoxicity models, possibly through redox regulation of some factors including CAT, BDNF, Hsp27, SOD, HO-1 and GPX-1.

alleviating glutathione depletion and increasing NADPH level (Pandey et al., 2016), demonstrating that Hsp27 plays a protective role in the CNS by modulating ROS levels; this is supported by findings in hippocampal progenitor cells, which were thus protected from glucocorticoid-induced apoptosis (Liang et al., 2018). However, Hsp27 silencing reduced apoptosis and ROS levels in an *in vitro* model of colorectal cancer, suggesting that the mechanism by which Hsp27 regulates cellular redox status is complex. In the striatum of rat, METH challenge increased *BDNF* mRNA expression but had the opposite effect after METH preconditioning (Cadet et al., 2011). Thus, mesencephalic dopaminergic and striatal non-dopaminergic neurons differ in their sensitivity to the effects of METH preconditioning. The upregulation of BDNF in midbrain dopaminergic neurons may increase BDNF release in the striatum, with a compensatory downregulation of BDNF in striatal cells via epigenetic modification (Dennis and Levitt, 2005). BDNF exerts antioxidant effects by preventing the accumulation of the lipid peroxidation product 4-hydroxynonenal (Joosten and Houweling, 2004), implying a protective role for BDNF in METH preconditioning (Fig. 3).

Although many studies have shown the postconditioning effect that administration of low-dose METH after severe traumatic brain injury (TBI) improves cognitive and motor impairment via activation of DA/PI3K/AKT signaling (Rau et al., 2011, 2012, 2014, 2016), the benefits of METH preconditioning have not been extensively investigated in the context of neurological disorders such as neurodegenerative diseases, TBI and stroke. Further investigation is warranted to clarify the effects of and mechanism underlying METH preconditioning in CNS diseases.

5. Summary and conclusions

Redox homeostasis is essential for organisms to maintain normal biological function, especially in the brain; disruption of redox balance can lead to ischemic stroke and neurodegenerative diseases (Franco and Vargas, 2018; Lu et al., 2019; Sies, 2015). EtOH, morphine, and METH are frequently abused neurotoxic substances that stimulate ROS production and cause neuronal injury (Chastain and Sarkar, 2014; Samikkannu et al., 2015; Yang et al., 2018); however, there is limited evidence for neuropathology caused by exposure to low doses of METH

Table 1
The summary of the anti-oxidative effects of EtOH, morphine and METH in brain disease models.

Agents	Species	Dosing regimen	Key results	References
EtOH	Gerbil model of transient global cerebral ischemia	0.48 g/kg i.g for 24 h	increased NOX activity and induced the formation of ROS from NOX	Wang et al. (2007)
	Mice mode of transient global cerebral ischemia	0.48 g/kg i.g for 24 h	activated BK_{Ca} channel	Wang et al. (2010)
	Rat primary cortical neurons	10 mM for 24 h	activated BK_{Ca} channel, attenuated the OGD/R-induced cytosolic of Ca^{2+}, up-regulated Bcl-2 and down-regulated Bax	Su et al. (2017)
	Rat cerebellar mixed cultures	30 mM for 2 d, 6 d	increased the synaptic localization and activity of NMDAR	Mitchell et al. (2009)
	Rat cerebellar mixed primary cultures	30 mM for 2 d, 6 d	increased the synaptic localization and activity of NMDAR and enhanced the level of antioxidant protein Prx2	Mitchell et al. (2016)
	Rat pups cerebellar neuronal/glial cultures	30 mM for 3 d	up-regulated NMDAR-PKC-Prx2	Khodaie et al. (2018)
	Rat pups cerebellar mixed cell and organotypic HEC slice cultures	30 mM for 6 d	increased the activity of PKC-FAK/p-FAK-Hsp27/p-Hsp27 and Hsp70	Sivaswamy et al. (2010)
	Rat pups organotypic HEC slice cultures	30 mM for 6 d	increased the level of Hsp70	Belmadani et al. (2003)
	Rat organotypic HEC slice cultures	20–30 mM for 6 d	reduced the level of $O_2^{\cdot-}$ and AA	Belmadani et al. (2001)
	HT22 cell	17 mM for 6 h, 24 h, 30 h and 48 h	increased the gene expression and enzyme activity of antioxidant proteins such as SOD, GPX, GSR and TrxR	Casanas-Sanchez et al. (2016)
Morphine	C8-B4 cell	0–10 μM for 30 min	activated δ_1ODR and inhibited the expression of iNOS	Gwak et al. (2010)
	Rat cerebellar brain slice	3 μM for 30 min	activated δ_1ODR and activated mK_{ATP} channel and inhibited the level of ROS induced by OGD/R	Lim et al. (2004)
	BULB/c mice	10 mg/kg/day to 30 mg/kg/day s.c. for 5 d	activated δ_1ODR and activated mK_{ATP} channel and increased the expression of Bcl-2 and CAT and decreased the expression of Bax and MDA	Arabian et al. (2017)
	SH-SY5Y cell	50 or 100 μM for 30 min	reducd the intracellular ROS, Ca^{2+} and attenuated the depression of the MMP	Elyasi et al. (2014)
	SH-SY5Y cell	50 μM for 30 min	reducd the intracellular ROS, Ca^{2+} and attenuated the depression of the MMP	Elyasi et al. (2019)
	SH-SY5Y cell	50 μM for 24 h	improved mitochondria dysfunction and suppressed the accumulation of intracellular ROS	Wang et al. (2018)
	Human primary neurons	1 μM for 5 d	activated ODR and down-regulated Bax and Hsp70	Cui et al. (2008)
	Mice primary cortical neurons cultures	3 μM for 1 h	down-regulated the expression of miR-134	Meng et al. (2016)
	BALB/c mice	10 mg/kg/day to 30 mg/kg/day s.c. for 5 d	increased the level of p-mTOR and the activity of SOD	Arabian et al. (2018)
	BALB/c mice	10 mg/kg/day to 30 mg/kg/day for 5 days	activated δ_1ODR and the production of NO	Arabian et al. (2015)
METH	Rat	0.5 mg/kg/day to 14 mk/kg/day i.p. for 2 w	attenuation of METH-induced striatal DA depletion but not consistent attenuation of 5-HT	Graham et al. (2008)
	Rat	2.5 mk/kg x 5, 5.0 mg/kg x 5 and 7.5 mg/kg x 5 at 6 h intervals s.c	protected against the DA and 5-HT depletion induced by METH	Danaceau et al. (2007)
	Rat	0.5 mg/kg/day to 14 mg/kg/day i.p. for 2 w	protected against METH challenge caused DA deletion in the striatum, and 5-HT depletion in the cortex	Cadet et al. (2009a)
	Rat	1.0 mg/kg/day to 10 mg/kg/day i.p. for 2 w	protected against METH challenge-induced DA and 5-HT depletion in the striatum and hippocampus	Hodges et al. (2011)
	Rat	0.1–4.0 mg/kg s.c. for 2 w	attenuated increases in core temperature induced by METH challenge and reductions in DAT binding and the DA response	O'Neil et al. (2006)
	Rat	0.5 mg/kg/day to 14 mk/kg/day i.p. for 2 w	altered midbrain transcriptional responses such as Hsp27, BDNF, CuZnSOD, GPX-1, HO-1	Cadet et al. (2009b)
	Rat	0.5 mg/kg/day to 14 mk/kg/day i.p. for 2 w	caused differential expression in different sets of striatal genes such as Hsp27, BDNF, HO-1	Cadet et al. (2011)
	Rat	1 mg/kg/day for 5 d	enhanced movement and neural activity	Takeichi et al., 2019
	MN9D cell	0.5 mM for 24 h	attenuated the decline in ATP levels and in mitochondrial dehydrogenase activity, and prevented the nuclear condensation	El Ayadi and Zigmond (2011)

and EtOH (Collins et al., 2009; Rau et al., 2016), and preconditioning with low doses may actually protect against the toxicity of these substances through antioxidant mechanisms (Table 1). Studies on the effects of chronic morphine treatment have yielded conflicting findings. For example, chronic morphine treatment (20 mg/kg for 12 days) in mice induced neuronal apoptosis in the hippocampus and impaired spatial memory (Lu et al., 2010), and rats treated with morphine (2.5, 5, and 7.5 mg/kg for 3 days) showed spatial memory dysfunction and decreased neuronal density in the hippocampus (Jahanshahi et al., 2014). These observations are inconsistent with the beneficial effects of morphine preconditioning; evaluating the effects of specific doses of morphine could resolve this contradiction.

Antioxidant therapy has beneficial effects in many brain disease models, and the therapeutic potential of antioxidant agents such as coenzyme Q (CoQ) and melatonin has been widely investigated in animal and cell models (Nyariki et al., 2019; Shah et al., 2019). For example, oral administration of CoQ10 protected mice with cerebral malaria against oxidative stress (Nyariki et al., 2019). Melatonin protects against middle cerebral artery occlusion-induced neuronal loss via NR2A-mediated pro-survival pathways (Shah et al., 2019). Treatment with antioxidants (e.g., butylated hydroxytoluene) reversed changes in the brain associated with EtOH-induced oxidative stress (Collins and Neafsey, 2012). In rat hippocampus, curcumin mitigated neuronal damage associated with morphine dependence via antioxidant and anti-apoptotic mechanisms (Motaghinejad et al., 2015). Similarly, the antioxidant functions of hydrogen sulfide and crocin inhibited the apoptosis of hippocampal neurons in the presence of METH (Ghanbari et al., 2019; Shafahi et al., 2018; Yang et al., 2019). However, most antioxidant therapies have failed to achieve curative effects in clinical trials. For example, although CoQ10 reduced the loss of DA neurons in a preclinical PD model, there was no evidence of clinical benefits in early PD patients (Parkinson Study Group et al., 2014). This could be due to the difficulty in delivering antioxidants to brain cells or the instability of these compounds. Stimulating the production of endogenous antioxidants through preconditioning is a potentially effective treatment strategy (Franco et al., 2019).

The neuroprotective effects associated with toxic substances are similar to those of ischemic preconditioning (Secondo et al., 2019), which is an adaptive response that prevents tissue injury but causes stress and trauma to target organs and major vessels. In contrast, pharmacological preconditioning confers protection without direct stress to organs (Suyavaran and Thirunavukkarasu, 2017; Tapuria et al., 2008). However, given the neurotoxicity of these substances and the fact that preconditioning is often affected by drug concentration, it is important to establish the duration of protection after the toxic insult. Another point that must be considered is whether pharmacological agents that do not induce tolerance after repeated administration can deliver therapeutic benefits over a wide range of doses (Mabrouk, 2018).

Signaling pathways such as Hippo, tuberous sclerosis 1 (Tsc1)/Tsc2, Kelch-like ECH-associated protein 1/Nrf2, forkhead box O1, Wnt/β-catenin, Janus kinase 2/signal transducer and activator of transcription 3, and a disintegrin and metalloproteinase with thrombospondin motif 1 as well as the ubiquitin-proteasome system (i.e., extracellular signal-regulated kinase 5) are involved in oxidative metabolism in stroke and AD models (Amani et al., 2019; Cao et al., 2019; Liu et al., 2017). EtOH, morphine, and METH may affect neuronal fate by these or as yet unidentified signaling pathways that must be elucidated in order to achieve the full clinical benefits of preconditioning.

Conflicts of interest

The authors declare there is no potential conflict of interests.

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Abbreviation

i.g.: gavage
i.p.: intraperitoneally injected
s.c.: subcutaneous injection
AA: arachidonic acid
ATP: adenosine triphosphate
Bcl-2: B cell lymphoma 2
Bax: Bcl-2-associated X protein
BDNF: brain derived neurotrophic factor
BK_{Ca} channel: large conductance calcium-activated potassium channel
CAT: catalase
DA: dopamine
DAT: dopamine transporter
EtOH: ethanol
FAK: focal adhesion kinase
GPX: glutathione peroxidase
GSR: glutathione-S-reductase
Hsp: heat shock protein
HO-1: heme oxygenase-1
5-HT: serotonin
MDA: malondialdehyde
METH: methamphetamine
mK_{ATP} channel: mitochondrial adenosine triphosphate-sensitive potassium channel
MMP: mitochondrial membrane potential
mTOR: Mammalian target of rapamycin
NO: nitric oxide
NOX: NADPH oxidase
$O_2^{\cdot}$: superoxide
OGD/R: oxygen glucose deprivation/ reperfusion
δ_1ODR: δ_1 opioid receptor
PKC: protein kinase C
Prx2: peroxiredoxin-2
ROS: reactive oxygen species
SOD: superoxide dismutase
TrxR: thioredoxin reductase