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Linking cocaine to endoplasmic reticulum in striatal neurons: role of glutamate receptors

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Abstract

The endoplasmic reticulum (ER) controls protein folding. Accumulation of unfolded and misfolded proteins in the ER triggers an ER stress response to accelerate normal protein folding or if failed to cause apoptosis. The ER stress response is a conserved cellular response in mammalian cells and is sensitive to various physiological or pathophysiological stimuli. Recent studies unravel that this response in striatal neurons is subject to the tight modulation by psychostimulants. Cocaine and amphetamines markedly increased expression of multiple ER stress reporter proteins in the dorsal striatum (caudate putamen) and other basal ganglia sites. This evoked ER stress response is mediated by activation of group I metabotropic glutamate receptors and *N*-methyl-D-aspartate receptors. Converging Ca²⁺ signals derived from activation of these receptors activate the c-Jun N-terminal kinase pathway to evoke ER stress responses. The discovery of robust ER stress responses to stimulant exposure establishes a previously unrecognized stimulant-ER coupling. This inducible coupling seems to contribute to neurotoxicity of stimulants related to various neuropsychiatric and neurodegenerative illnesses. Elucidating cellular mechanisms linking cocaine and other stimulants to ER is therefore important for the development of therapeutic agents for treating neurological disorders resulted from stimulant toxicity.

Keywords

caudate putamen; mGluR; NMDA; chaperone; UPR; BiP; JNK; psychostimulant

Introduction

The endoplasmic reticulum (ER) is a subcellular structure responsible for folding and processing proteins. Accumulation of unfolded or misfolded proteins in the lumen of the ER activates the ER stress response, otherwise known as the unfolded protein response (UPR), a cellular response to stress conserved in all mammalian species. Once activated, the UPR plays dual roles. It initially aims to restore normal cellular function by halting protein translation and activating the signaling pathways for a higher production of molecular

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Conflict of interests

No conflict of interests for all authors.

chaperones involved in normal protein folding. If this restoration effort fails to achieve its goal timely or the stress response is prolonged, the UPR aims to apoptosis [1–3]. The ER stress response, as a conserved protective mechanism, is sensitive to a variety of physiological and pathophysiological stimuli. It ensures normal cell function and survival. On the other hand, malfunction of this response causes cell injury or death and contributes to the pathogenesis of various neurological disorders, including stroke, neurotrauma, and epileptic seizures, and neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's diseases, and amyotrophic lateral sclerosis [4,5]. Noticeably, emerging evidence from this laboratory and others links ER activity to drugs of abuse.

Cocaine, an indirect dopamine receptor agonist, is a powerful agent regulating glutamatergic transmission in the central nervous system. In the striatum, cocaine regulates glutamate release and increases extracellular levels of the transmitter. This regulation is mediated through trans-synaptic circuits in the basal ganglia, while it also depends on the responsivity of several intracellular signaling molecules to cocaine [6,7]. Increased glutamate interacts with group I metabotropic glutamate receptors (i.e., mGluR1 and mGluR5 subtypes) that are coupled to the intracellular Ca^{2+} pathway and *N*-methyl-D-aspartate (NMDA) receptors that are Ca^{2+} permeable. Interactions with these postsynaptic glutamate receptors dynamically alter cytoplasmic Ca^{2+} homeostasis in striatal neurons. Altered Ca^{2+} signals may then readily cause a Ca^{2+} -sensitive ER stress response. Indeed, available data from recent studies provide emerging evidence for the cocaine-stimulated ER stress response in striatal neurons [8,9]. These responses may reflect a plastic change contributing to the addictive properties of cocaine or neurotoxic effects of stimulants. This review will summarize the evidence from these studies and will further analyze the role of group I mGluRs and NMDA receptors in linking cocaine to the ER stress response.

Key ER stress proteins

Multiple ER-associated proteins are involved in the ER stress response. Immunoglobulin heavy chain binding protein (BiP) is a well-known ER chaperone that aids the protein folding and acts as a sensitive ER stress sensor. BiP controls activity of multiple downstream transducers, such as inositol-requiring enzyme-1 α (Ire1 α), ATF6, and perk of the UPR signaling pathway [10]. Among these transducer proteins, Ire1 α and perk appear to be responsible for initiating the UPR [11]. At the state of the ER stress, a series of changes occur, including hyper-phosphorylation of eIF2 α , up-regulation of GPR78, increased expression of GADD153/ C/EBP-homologous protein (CHOP), and cleavage of procaspase-12 in non-neuronal cells [12]. These changes are essential for protecting against apoptotic processes [13], and are considered to be cellular reporters of the occurrence of the ER stress response.

Given that the ER stress response to psychostimulants in the brain has been barely analyzed, Shin and co-workers made an attempt to investigate the possible impact of cocaine on the ER stress response in rat striatal neurons *in vivo* [9]. They found that repeated cocaine administration increased expression of several ER stress proteins (BiP, CHOP, and Ire1 α) in the rat dorsal striatum/caudate putamen. Acute injection of cocaine also induced a transient induction of ER stress proteins in the striatum. These results are consistent with those from the studies using another psychostimulant methamphetamine. A non-contingent injection of methamphetamine induced a delayed and prolonged increased in BiP and CHOP expression in the mouse striatum [14]. Operant self-administration of methamphetamine also increased BiP expression in the rat VTA and substantia nigra [15]. Several genes that are regulated during ER stress, namely ATF3, HSP27, Hmox1, and HSP40, were also increased in response to methamphetamine [16]. These data collectively suggest that psychostimulants represent a group of effective activators of the ER stress response in striatal neurons.

How cocaine and amphetamines stimulate the ER stress response is unclear. At the receptor level, dopamine D1 receptors are required to mediate the effect of cocaine. Pretreatment with the dopamine D1 receptor antagonist blocked cocaine-stimulated stress protein expression in the striatum [16]. In addition to dopamine signaling, available data show the role of group I mGluRs in mediating this event. Group I mGluRs are coupled to phospholipase C (PLC) via Gαq proteins. Activation of these receptors results in the inositol-1,4,5-triphosphate (IP₃)-dependent release of Ca²⁺ from intracellular stores and activation of protein kinase C. The majority of medium spiny output neurons, i.e., striatonigral and striatopallidal projection neurons, in the dorsal striatum express group I mGluRs [17–21]. Activation of these receptors appears to be required for cocaine-stimulated induction of ER stress proteins because pharmacological blockade of group I mGluRs with a group I mGluR selective antagonist reduced the upregulation of striatal ER stress proteins in response to cocaine [9]. Cocaine stimulation has been demonstrated to increase extracellular levels of glutamate in the local striatum. Increased glutamate may stimulate group I mGluRs to enhance intracellular Ca²⁺ signals. This upregulated group I mGluR-Ca²⁺ pathway may eventually participate in the cocaine-stimulated ER stress response.

In addition to group I mGluRs, NMDA receptors are critical for mediating the cocaine's impact on ER stress responses. As Ca²⁺-permeable and ligand-gated ion channels, activation of NMDA receptors triggers Ca²⁺ influx to modify a number of Ca²⁺-sensitive signaling pathways [22,23]. Like group I mGluRs, NMDA receptors are abundantly expressed in striatal projection neurons [24–26]. Stimulation of these receptors is seemingly required for the cocaine-ER coupling since the NMDA receptor antagonist decreased the BiP expression in the dorsal striatum induced by repeated cocaine administration [9]. Given the fact that group I receptors and NMDA receptors both play significant roles, the two receptors may act in concert to regulate ER stress responses. Group I mGluRs and NMDA receptors may synergistically raise intracellular Ca²⁺ concentrations to a level sufficient to induce ER stress responses.

Additionally, group I mGluRs have long been appreciated to potentiate NMDA receptor activity. Initial activation of group I mGluRs may serve to potentiate the final NMDA receptor pathway to induce ER stress responses. How group I mGluR- and NMDA receptor-dependent Ca²⁺ signals induce ER stress responses is unclear. It is believed that Ca²⁺-sensitive protein kinase signaling cascade(s) are involved in transmitting Ca²⁺ signals to ER (see below).

Caspase-12

In addition to the ER stress proteins mentioned above, caspase-12 is another sensitive target of cocaine. Caspase-12 is a specific ER-resident caspase and is activated in ER stress responses in neurons and non-neuronal glial cells [27–29]. It plays an important role in activation of apoptosis-inducing factor (AIF) via the Ca²⁺-mediated protein misfolding in cultured cells [30]. In attempting to explore the effect of cocaine on caspase-12 expression, we found that acute and repeated administration of cocaine induced robust expression of this protein in the rat dorsal striatum [8]. Acute injection of methamphetamine also activated caspase-12 in the mouse striatum [14]. These results indicate that caspase-12 is among ER stress proteins that are sensitive to stimulant exposure. The cocaine linkage to caspase-12 involves activation of NMDA receptors. Microinjection of the NMDA receptor antagonists into the dorsal striatum attenuated the caspase-12 expression induced by repeated administration of cocaine. However, the NMDA receptor antagonists were ineffective in affecting caspase-12 expression induced by acute cocaine injection. Thus, NMDA receptors seem to be preferentially involved in the response of caspase-12 to repeated cocaine administration.

Poly(ADP-ribose) polymerase-1 (PARP-1)

PARP-1 is a ubiquitous and abundant nuclear protein and the founding member of the PARP family. It is also an important factor involved in apoptotic cell death in the central nervous system [31–33]. PARP-1 is known to repair a genome when the degree of DNA damage is moderate [32]. In the presence of massive DNA damage, PARP-1 enters a state of overactivation [32]. This overactivation causes the translocation of AIF from the mitochondria to the nucleus, leading to caspase-independent apoptosis in neurons and non-neuronal cells [31]. Several recent studies show the association of PARP-1 expression and activity with the ER stress in striatal neurons. Repeated exposure to cocaine activated PARP-1 in the dorsal striatum [34]. Similarly, acute and repeated cocaine administration upregulated PARP-1 expression in cultured fetal locus coeruleus and fetal mouse cerebral cortex [35,36]. However, only repeated, but not acute, cocaine administration upregulated expression of the cleaved form (active form) of PARP-1 in the rat dorsal striatum [34]. This indicates that repeated exposure to cocaine may be required to fully activate PARP-1. The Ca^{2+} mobilization evoked by the PLC/IP3 pathway activated PARP-1 in cortical neurons [37], establishing a new mechanism to activate PARP-1 in addition to severe DNA damage. Consistent with this, blockade of mGluR1, although not mGluR5, reduced the increase in cleaved PARP-1 expression in striatal neurons following repeated cocaine injections [34]. Thus, the mGluR1-sensitive PLC/IP3 pathway is involved in mediating the response of PARP-1 to cocaine. NMDA receptors are also important for cocaine-mediated activation of PARP-1 since the NMDA receptor antagonists reduced the PARP-1 activation by cocaine [34]. Nitric oxide can also regulate PARP-1 activity. Repeated cocaine administration induced a group I mGluR- and NMDA receptor-dependent nitric oxide efflux in the striatum [38]. Thus, these receptors can also link cocaine to PARP-1 via the nitric oxide-sensitive pathway.

It is interesting to note that caspase-12 activation by methamphetamine led to the upregulation of cleaved PARP-1 expression in the mouse striatum [14]. This suggests that stimulants can activate PARP-1 via a mechanism involving the ER stress response. By blocking the ER stress response to stimulants, the group I mGluR and NMDA receptor antagonists can thereby reduce downstream activation of PARP-1. Adaptive alterations in PARP-1 activity may be an essential component in overall chronic cocaine-associated ER stress responses. It acts in concert with other ER stress proteins to control neurotoxic effects of stimulants in striatal neurons.

A signaling pathway linking cocaine to ER

An attempt has been made to identify an intracellular signaling pathway that transmits glutamate receptor signals to the ER stress response in response to cocaine [39]. The data underscore the importance of a c-Jun N-terminal kinase (JNK)-dependent pathway. JNK is a subclass of the mitogen-activated protein kinase family and can form a superhighway transmitting receptor signals to the distinct intracellular microdomain and activity in striatal neurons [40]. Repeated cocaine administration increased phosphorylation (i.e., activation) of JNK in the dorsal striatum, although acute injection of the drug did not [39]. The activation of JNK is believed to be mediated by glutamate receptors. The group I mGluR and NMDA receptor antagonists reduced JNK phosphorylation induced by cocaine [39]. Direct activation of group I mGluRs or NMDA receptors increased JNK phosphorylation in striatal or cortical neurons via a Ca^{2+} -sensitive manner [41–43]. Thus, cocaine, through activating group I mGluRs and NMDA receptors, increases JNK activity in striatal neurons. This increase in JNK activity seems to be an important and sequential step leading to the upregulation of the ER stress proteins (BiP and caspase-12) because inhibition of JNK with the selective inhibitor attenuated the induction of these proteins [39]. Taken together, the

above results suggest a model that the JNK pathway is activated in response to cocaine through a group I mGluR- and NMDA receptor-dependent way. Active JNK is then engaged to regulate the ER stress response.

Implications of stimulant-ER coupling

The implication of the newly discovered stimulant-ER coupling is twofold. Firstly, the induced ER stress response may participate in neuroadaptations important for the addictive properties of drugs of abuse. At present, to our knowledge, no attempt has been made to explore this intriguing topic. It is possible that repeated stimulant exposure progressively augments ER stress responses to modulate the folding process of certain proteins, including receptors, transporters, enzymes, and structural proteins. This in turn causes plastic changes in protein expression, distribution, and function, leading to enduring drug addiction. Protein targets regulated by the stimulant-ER coupling are unknown. Future studies will have to elucidate the implication of the coupling in the regulation of a specific protein and in drug addiction [15]. Secondly, compared to the lack of investigations on roles in drug addiction, there is evidence showing a significant implication of the stimulant-ER association in neurotoxicity. It has been well documented that amphetamine and methamphetamine insults cause robust neurotoxicity in the central nervous system [44–46]. This neurotoxicity is often associated with oxidative stress, mitochondrial dysfunction, excitotoxicity, and inhibition of neurogenesis [45,46]. In addition, the ER stress-associated apoptotic pathway is an effective route leading to neuroblastoma cell and neuron death [14,47,48]. Thus, it is possible that the ER apoptotic pathway could contribute at least in part to stimulant-induced neurotoxicity. In fact, systemic injections of methamphetamine induced immediate activation of proteases calpain and caspase-12 and increases in BiP and CHOP expression in rat striatal neurons, events consistent with drug-induced ER stress [14,16]. These events preceded proteolysis of the caspase substrates DFF-45, lamin A, and PARP in nuclear fractions. Blocking induction of ER stress proteins reduced methamphetamine-induced neuronal apoptosis [16]. Thus, methamphetamine causes neuron injury in part via ER stress- and mitochondria-generated apoptotic processes.

Conclusions

The ER stress response is a conserved cellular response to multiple stimuli. Recent studies reveal that this response in striatal neurons is subject to the modulation by psychostimulants. Acute or repeated administration of cocaine and methamphetamine markedly increased expression of ER stress proteins. As to receptors and associated signaling pathways that mediate the effect of stimulants on the ER stress response, glutamate receptors and the JNK pathway seem to play a significant role. As described in Fig. 1, cocaine stimulation results in an increase in local glutamate release. Increased glutamate induces intracellular Ca^{2+} rises in striatal medium spiny neurons possibly through three routes: 1) group I mGluR-mediated activation of the PLC/IP3 pathway, which releases Ca^{2+} from the ER, 2) NMDA receptor-mediated Ca^{2+} influx, and 3) group I mGluR-mediated activation of the DAG/PKC pathway, which phosphorylates NMDA receptors and thus potentiates their activity. Increased Ca^{2+} signals can activate JNK to upregulate expression of ER stress proteins such as BiP and caspase-12. Active caspase-12 can further lead to activation of PARP-1 to join a stepwise ER stress response. Repeated exposure to stimulants may overly stimulate this ER stress response, leading to neuron damage. This ER stress response to stimulant exposure may contribute to neurotoxicity of stimulants related to various neuropsychiatric and neurodegenerative illnesses. Elucidating mechanisms linking cocaine to ER is therefore important for the development of therapeutic agents for treating neurological disorders derived from cocaine toxicity.

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Abbreviations

AIF	apoptosis-inducing factor
BiP	immunoglobulin heavy chain binding protein
CHOP	C/EBP-homologous protein
ER	endoplasmic reticulum
Glu	glutamate
IP₃	inositol-1,4,5-triphosphate
Ire1α	inositol-requiring enzyme-1 α
JNK	c-Jun N-terminal kinase
mGluRs	metabotropic glutamate receptors
NMDA	<i>N</i> -methyl-D-aspartate
PARP-1	poly(ADP-ribose) polymerase-1
PLC	phospholipase C
UPR	unfolded protein response

References

1. Katayama T, Imaizumi K, Manabe T, Hitomi J, Kudo T, Tohyama M. Induction of neuronal death by ER stress in Alzheimer's disease. *J Chem Neuroanat.* 2004; 28:67–78. [PubMed: 15363492]
2. Ermak G, Davies KJ. Calcium and oxidative stress: from cell signaling to cell death. *Mol Immunol.* 2002; 38:713–721. [PubMed: 11841831]
3. Kaufman RJ. Stress signaling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls. *Genes Dev.* 1999; 13:1211–1233. [PubMed: 10346810]
4. Paschen W, Mengesdorf T. Endoplasmic reticulum stress response and neurodegeneration. *Cell Calcium.* 2005; 38:409–415. [PubMed: 16087231]
5. Paschen W. Endoplasmic reticulum dysfunction in brain pathology: critical role of protein synthesis. *Curr Neurovasc Res.* 2004; 1:173–181. [PubMed: 16185192]
6. Rahman MA, Kwon NH, Won MS, Choe ES, Shim YB. Functionalized conducting polymer as an enzyme immobilizing substrate: an amperometric glutamate microbiosensor for in vivo measurements. *Anal Chem.* 2005; 77:4854–4860. [PubMed: 16053298]
7. Kalivas PW, McFarland K, Bowers S, Szumlanski K, Xi ZX, Baker D. Glutamate transmission and addiction to cocaine. *Ann N Y Acad Sci.* 2003; 1003:169–175. [PubMed: 14684444]
8. Ahn SM, Kim SW, Choe ES. Cocaine increases immunoglobulin heavy chain binding protein and caspase-12 expression in the rat dorsal striatum. *Psychopharmacology (Berl).* 2007; 195:407–414. [PubMed: 17849098]
9. Shin EH, Bian S, Rahman MA, Shim YB, Chung KT, Kim JY, Wang JQ, Choe ES. Cocaine increases endoplasmic reticulum stress protein expression in striatal neurons. *Neuroscience.* 2007; 145:621–630. [PubMed: 17303341]
10. Ma Y, Hendershot LM. Herp is dually regulated by both the endoplasmic reticulum stress-specific branch of the unfolded protein response and a branch that is shared with other cellular stress pathways. *J Biol Chem.* 2004; 279:13792–13799. [PubMed: 14742429]

11. Miyoshi K, Katayama T, Imaizumi K, Taniguchi M, Mori Y, Hitomi J, Yui D, Manabe T, Gomi F, Yoneda T, Tohyama M. Characterization of mouse Ire1 alpha: cloning, mRNA localization in the brain and functional analysis in a neural cell line. *Brain Res Mol Brain Res*. 2000; 85:68–76. [PubMed: 11146108]
12. Liu N, Kuang X, Kim HT, Stoica G, Qiang W, Scofield VL, Wong PK. Possible involvement of both endoplasmic reticulum- and mitochondria-dependent pathways in MoMuLV-ts1-induced apoptosis in astrocytes. *J Neurovirol*. 2004; 10:189–198. [PubMed: 15204924]
13. Morris JA, Dorner AJ, Edwards CA, Hendershot LM, Kaufman RJ. Immunoglobulin binding protein (BiP) function is required to protect cells from endoplasmic reticulum stress but is not required for the secretion of selective proteins. *J Biol Chem*. 1997; 272:4327–4334. [PubMed: 9020152]
14. Jayanthi S, Deng X, Noailles PA, Ladenheim B, Cadet JL. Methamphetamine induces neuronal apoptosis via cross-talks between endoplasmic reticulum and mitochondria-dependent death cascades. *FASEB J*. 2004; 18:238–251. [PubMed: 14769818]
15. Hayashi T, Justinova Z, Hayashi E, Cormaci G, Mori T, Tsai SY, Barnes C, Goldberg SR, Su TP. Regulation of sigma-1 receptors and endoplasmic reticulum chaperones in the brain of methamphetamine self-administering rats. *J Pharmacol Exp Ther*. 2010; 332:1054–1063. [PubMed: 19940104]
16. Jayanthi S, McCoy MT, Beauvais G, Ladenheim B, Gilmore K, Wood W 3rd, Becker K, Cadet JL. Methamphetamine induces dopamine D1 receptor-dependent endoplasmic reticulum stress-related molecular events in the rat striatum. *PLoS One*. 2009; 4:e6092. [PubMed: 19564919]
17. Dev KK, Nakajima Y, Kitano J, Braithwaite SP, Henley JM, Nakanishi S. PICK1 interacts with and regulates PKC phosphorylation of mGluR7. *J Neurosci*. 2000; 20:7252–7257. [PubMed: 11007882]
18. Tallaksen-Greene SJ, Kaatz KW, Romano C, Albin RL. Localization of mGluR1a-like immunoreactivity and mGluR5-like immunoreactivity in identified populations of striatal neurons. *Brain Res*. 1998; 780:210–217. [PubMed: 9507137]
19. Kerner JA, Standaert DG, Penney JB, Young AB, Landwehrmeyer GB. Expression of group one metabotropic glutamate receptor subunit mRNAs in neurochemically identified neurons in the rat neostriatum, neocortex, and hippocampus. *Brain Res Mol Brain Res*. 1997; 48:259–269. [PubMed: 9332723]
20. Testa CM, Friberg IK, Weiss SW, Standaert DG. Immunohistochemical localization of metabotropic glutamate receptors mGluR1a and mGluR2/3 in the rat basal ganglia. *J Comp Neurol*. 1998; 390:5–19. [PubMed: 9456172]
21. Testa CM, Standaert DG, Landwehrmeyer GB, Penney JB, Young AB. Differential expression of mGluR5 metabotropic glutamate receptor mRNA by rat striatal neurons. *J Comp Neurol*. 1995; 354:241–252. [PubMed: 7782501]
22. Stephenson FA. Subunit characterization of NMDA receptors. *Curr. Drug. Targets*. 2001; 2:233–239. [PubMed: 11554550]
23. Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. *Pharmacol Rev*. 1999; 51:7–61. [PubMed: 10049997]
24. Chen Q, Veenman CL, Reiner A. Cellular expression of ionotropic glutamate receptor subunits on specific striatal neuron types and its implication for striatal vulnerability in glutamate receptor-mediated excitotoxicity. *Neuroscience*. 1996; 73:715–731. [PubMed: 8809793]
25. Landwehrmeyer GB, Standaert DG, Testa CM, Penney JB Jr, Young AB. NMDA receptor subunit mRNA expression by projection neurons and interneurons in rat striatum. *J Neurosci*. 1995; 15:5297–5307. [PubMed: 7623152]
26. Standaert DG, Testa CM, Penney JB, Young AB. Organization of N-methyl-D-aspartate glutamate receptor gene expression in the basal ganglia of the rat. *J Comp Neurol*. 1994; 343:1–16. [PubMed: 8027428]
27. Shimoke K, Utsumi T, Kishi S, Nishimura M, Sasaya H, Kudo M, Ikeuchi T. Prevention of endoplasmic reticulum stress-induced cell death by brain-derived neurotrophic factor in cultured cerebral cortical neurons. *Brain Res*. 2004; 1028:105–111. [PubMed: 15518647]

28. Chen L, Gao X. Neuronal apoptosis induced by endoplasmic reticulum stress. *Neurochem Res.* 2002; 27:891–898. [PubMed: 12396099]
29. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. *Nature.* 2000; 403:98–103. [PubMed: 10638761]
30. Sanges D, Marigo V. Cross-talk between two apoptotic pathways activated by endoplasmic reticulum stress: differential contribution of caspase-12 and AIF. *Apoptosis.* 2006; 11:1629–1641. [PubMed: 16820963]
31. Moroni F. Poly(ADP-ribose) polymerase 1 (PARP-1) and postischemic brain damage. *Curr Opin Pharmacol.* 2008; 8:96–113. [PubMed: 18032109]
32. Sammut S, Dec A, Mitchell D, Linardakis J, Ortiguera M, West AR. Phasic dopaminergic transmission increases NO efflux in the rat dorsal striatum via a neuronal NOS and a dopamine D (1/5) receptor-dependent mechanism. *Neuropsychopharmacology.* 2006; 31:493–505. [PubMed: 16012530]
33. Yu SW, Wang H, Dawson TM, Dawson VL. Poly(ADP-ribose) polymerase-1 and apoptosis inducing factor in neurotoxicity. *Neurobiol Dis.* 2003; 14:303–317. [PubMed: 14678748]
34. Yang JH, Choe ES. Repeated cocaine administration increases cleaved poly(ADP-ribose) polymerase-1 expression in the rat dorsal striatum. *Neurosci Lett.* 2010; 471:58–61. [PubMed: 20079403]
35. Dey S, Mactutus CF, Booze RM, Snow DM. Cocaine exposure in vitro induces apoptosis in fetal locus coeruleus neurons by altering the Bax/Bcl-2 ratio and through caspase-3 apoptotic signaling. *Neuroscience.* 2007; 114:509–521. [PubMed: 17084983]
36. Novikova SI, He F, Bai J, Badan I, Lidow IA, Lidow MS. Cocaine-induced changes in the expression of apoptosis-related genes in the fetal mouse cerebral wall. *Neurotoxicol Teratol.* 2004; 27:3–14. [PubMed: 15681117]
37. Homburg S, Visochek L, Moran N, Dantzer F, Priel E, Asculai E, Schwartz D, Rotter V, Dekel N, Cohen-Armon M. A fast signal-induced activation of Poly(ADP-ribose) polymerase: a novel downstream target of phospholipase c. *J Cell Biol.* 2000; 24:293–307. [PubMed: 10908573]
38. Lee DK, Koh WCA, Shim YB, Shim I, Choe ES. Repeated cocaine administration increases nitric oxide efflux in the rat dorsal striatum. *Psychopharmacology (Berl).* 2010; 208:245–256. [PubMed: 19936712]
39. Go BS, Ahn SM, Shim I, Choe ES. Activation of c-Jun N-terminal kinase is required for the regulation of endoplasmic reticulum stress response in the rat dorsal striatum following repeated cocaine administration. *Neuropharmacology.* 2010; 59:100–106. [PubMed: 20399218]
40. Wang JQ, Tang Q, Parelkar NK, Liu Z, Samdani S, Choe ES, Yang L, Mao L. Glutamate signaling to Ras-MAPK in striatal neurons: mechanisms for inducible gene expression and plasticity. *Mol Neurobiol.* 2004; 29:1–14. [PubMed: 15034219]
41. Yang L, Mao L, Chen H, Catavsan M, Kozinn J, Arora A, Liu X, Wang JQ. A signaling mechanism from G alpha q-protein-coupled metabotropic glutamate receptors to gene expression: role of the c-Jun N-terminal kinase pathway. *J Neurosci.* 2006; 26:971–980. [PubMed: 16421317]
42. Ko HW, Park KY, Kim H, Han PL, Kim YU, Gwag BJ, Choi EJ. Ca²⁺-mediated activation of c-Jun N-terminal kinase and nuclear factor kappa B by NMDA in cortical cell cultures. *J Neurochem.* 1998; 71:1390–1395. [PubMed: 9751169]
43. Schwarzschild MA, Cole RL, Hyman SE. Glutamate, but not dopamine, stimulates stress-activated protein kinase and AP-1-mediated transcription in striatal neurons. *J Neurosci.* 1997; 17:3455–3466. [PubMed: 9133371]
44. Nassogne MC, Louahed J, Evrard P, Courtoy PJ. Cocaine induces apoptosis in cortical neurons of fetal mice. *J Neurochem.* 1997; 68:2442–2450. [PubMed: 9166738]
45. Cadet JL, Krasnova IN, Jayanthi S, Lyles J. Neurotoxicity of substituted amphetamines: molecular and cellular mechanisms. *Neurotox Res.* 2007; 11:183–202. [PubMed: 17449459]
46. Cunha-Oliveira T, Rego AC, Oliverira CR. Cellular and molecular mechanisms involved in the neurotoxicity of opioid and psychostimulant drugs. *Brain Res Rev.* 2008; 58:192–208. [PubMed: 18440072]

47. Hetz C, Russelakis-Carneiro M, Maundrell K, Castilla J, Soto C. Caspase-12 and endoplasmic reticulum stress mediate neurotoxicity of pathological prion protein. *EMBO J.* 2003; 22:5435–5445. [PubMed: 14532116]
48. Ferreira E, Resende R, Costa R, Oliveira CR, Pereira CM. An endoplasmic-reticulum-specific apoptotic pathway is involved in prion and amyloid-beta peptides neurotoxicity. *Neurobiol Dis.* 2006; 23:669–678. [PubMed: 16844381]

Figure 1.

A schematic diagram illustrating cellular mechanisms underlying the cocaine-mediated regulation of the ER stress response in striatal medium spiny neurons. Putative interactions are discussed in detail in the text. Arrows represent the facilitatory regulation of downstream targets, while a blunt end represents the inhibitory regulation. DAG, diacylglycerol; Glu, glutamate; P, phosphorylation; PI, phosphoinositide; PKC, protein kinase C. See text for other abbreviations.