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COLLEGIUM INTERNATIONALE NEURO-PSYCHOPHARMACOLOGIUM (CINP) SYMPOSIUM: NEUROBIOLOGICAL BASE OF STIMULANT-INDUCED SENSITIZATION: FROM ANIMALS TO MAN

Chronic dopaminergic signaling in the basal ganglia: a damage perspective on kinases and fos-related antigens

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Abstract

Specific protein phosphorylation pathways have been shown to play a role in cellular adaptation responses underlying addiction to psychostimulants such as methamphetamine and cocaine. Transcriptional regulation through fos-related antigens constitutes one element through which these dopaminergic agonists exert their persistent actions. In addition to their addictive properties, amphetamines are known to damage dopaminergic nerve terminals. Although not widely appreciated, protein phosphorylation cascades and fos-related antigens also may play a role in the neurotoxic actions of substituted amphetamines such as methamphetamine. Here we document the involvement of the dopaminoceptive phosphoprotein, DARPP-32, the fos-related antigen, FRA–2, and the growth associated protein kinase, MAP kinase, in the neurotoxic action of known dopaminergic neurotoxicants, including methamphetamine. The addictive and neurotoxic properties of psychostimulants may share some molecular signaling mechanisms.

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Abbreviations

DARPP–32, dopamine and cyclic AMP-regulated phosphoprotein (M_r 32 kDa); FRA–2, fos-related antigen; PKA, protein kinase A; CREB, cAMP response element binding protein; VTA, ventral tegmental area; GFAP, glial fibrillary acidic protein; ERK, extracellular signal regulated protein kinase; STAT, signal transducers and activators of transcription; MPTP, 1-methyl–4-phenyl-1,2,3,6-tetrahydropyridine; METH, methamphetamine; MDMA, methylenedioxymethamphetamine; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; MAPK, mitogen activated protein kinase; CAM, calmodulin.

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Introduction

Protein phosphorylation represents the dominant mode of post-translational modification through which cell–surface receptors transduce extracellular signals. A variety of protein kinase/protein phosphatase cascades have been identified that control a diverse array of neural functions.[1] One such cascade involves the intracellular signaling pathways through which dopaminergic neurotransmission is mediated. Drug-induced alterations in dopaminergic neurotransmission and of specific phosphosphorylation reactions within dopaminergic signaling pathways have been shown to have profound functional consequences on the whole organism. For example, it is generally accepted that augmenting signaling through the mesolimbic dopaminergic pathway contributes to the reward (addictive) properties underlying the drug-seeking behavior associated with abused drugs, such as amphetamine and cocaine.[2–6] At least for the case of certain amphetamine derivatives, persistent dopaminergic signaling also is associated with another condition: damage to dopaminergic nerve terminals (dopaminergic neurotoxicity).[7,8] While drug addiction and neurotoxicity represent distinct outcomes associated with chronic dopaminergic stimulation, data are emerging that implicate some of the same kinase pathways and transcription factors, such as fos-related antigens (FRA), in both of these conditions. The type of response engendered by a particular drug administration paradigm may be specified by the induction of a particular transcription factor. This, in turn, would allow for different gene expression patterns to be associated with drug addiction and neurotoxicity. Some aspects of the molecular signaling events common to these drug-induced effects will be reviewed below.

Molecular adaptations to chronic exposure to drugs of abuse

Cocaine and substituted amphetamines represent the prototypical drugs of abuse that serve as stimulants of dopamine neurotransmission in forebrain dopamine terminal fields, primarily the nucleus accumbens and the neostriatum.[9] The increase in extracellular dopamine caused by cocaine and amphetamines is thought to underlie the rewarding as well as the locomotor stimulant effects of these compounds following their acute or chronic administration, notwithstanding the fact that other pathways (e.g. serotonin) may also play a role[10] The action of psychomotor stimulants that has received the most attention over the past decade is the propensity to induce sensitization or "reverse" tolerance.[11] This involves the progressive enhancement of behavioral hyperactivity that is elicited by repeated exposure to psychostimulants such as cocaine and the amphetamines.[12] In this context, the reinforcing aspects of psychostimulant action in experimental animals serves as a model for the "rewarding" or reinforcing effects of drugs self-administered by humans.[13,14]

Over the past decade, Nestler and colleagues[4–6,15,16] have accumulated a large body of evidence that has contributed a great deal to our understanding of the molecular adaptations that occur following chronic administration of drugs of abuse (Fig. 1). Not only is the mesolimbic dopaminergic system strongly implicated in these responses, so too are expected (as well as some unexpected) changes in the protein phosphorylation pathways found in this brain region. For example, chronic dopaminergic stimulation of its receptors in the nucleus accumbens stimulates adenylate cyclase resulting in the production of cAMP and subsequent activation of PKA. PKA in turn catalyzes the phosphorylation, induction and enhanced AP–1 binding of the transcription factors, such as CREB, fos and the fos-like proteins collectively known as the chronic FRAs.[6,17–22] Of the transcription factors examined, the chronic FRAs have been most closely linked to effects of chronic drug administration. The chronic FRAs are isoforms of a variant of the *fosB* gene known as delta FosB.[2] Because delta FosB lacks the DNA activation domain of FosB,[23] it may actually act as a transcriptional inhibitor. The genes targeted by the chronic FRAs and other transcription factors remain unclear but they are likely to be numerous and involve complex interactions. For example, through a feedback mechanism not fully understood, chronic exposure to cocaine leads to an induction of tyrosine hydroxylase in the dopaminergic neurons of the VTA, an effect that potentially could play a strong role in the rewarding properties of drugs of abuse.[5] Unexpectedly, a number of surprising effects accompany this induction of tyrosine hydroxylase including an increase in the astrocyte intermediate filament protein, GFAP, and decreases in the levels of the neurofilament triplet proteins, whereas no effects are seen with respect to other cytoskeletal ele-

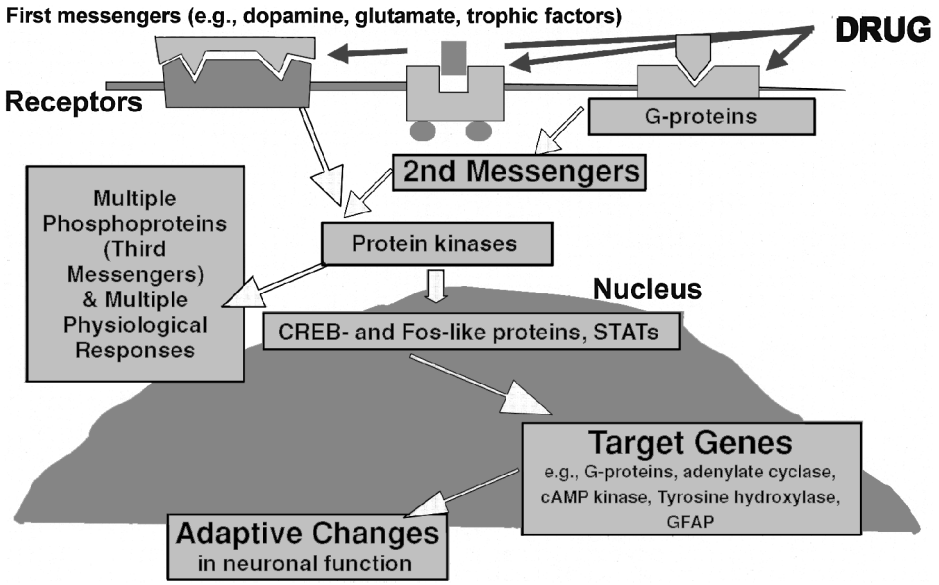

Figure 1. *Signal transduction pathways involved in molecular adaptations to drugs of abuse. CREB, cAMP response element binding protein; STAT, signal transducers and activators of transcription; GFAP, glial fibrillary acidic protein. Figure adapted from Nestler* et al.[15].

ments of the VTA.[4] Added to this complexity are the more recent findings that implicate glutamate receptor subunit phosphorylation in the chronic, but not the acute effects of cocaine[24] as well as an involvement of the neurotrophin-mediated activation of the ERK[25] and JAK-STAT pathway in the VTA.[26] Together these findings underscore the central role of protein phosphorylation and enhanced gene expression in the molecular events underlying drug addiction. As emphasized by Nestler and colleagues,[4,5] however, the involvement of multiple signaling pathways in the chronic effects of drugs of abuse suggests that the mechanisms underlying drug-seeking behavior are likely to be very complex.

Protein phosphorylation, FRAs and dopaminergic neurotoxicity

Alterations in protein kinases, protein phosphatases and their specific substrates have been implicated in a variety of neurological disease states.[27,28] Given the central role of protein phosphorylation in the regulation of many central nervous system processes, from receptor activation to gene expression, this is not surprising. Until recently, however, little attention has been given to the potential role of altered protein phosphorylation in the mediation of chemically induced neurotoxicity.[27,28] Recent findings now support a role of specific kinases, phosphatases and their substrates in neurotoxic responses, including those involving dopaminergic neurons. Moreover, some of the same signaling pathways linked to the addicting properties of drugs with primary actions on mesolimbic dopaminergic neurons appear to be affected in the nigrostriatal dopaminergic pathway by dopaminergic neurotoxicants. One prominent example is the role of the phosphatase inhibitor, DARPP–32[29,30] in methamphetamine neurotoxicity.

DARPP–32 and amphetamine neurotoxicity

One of the most well-characterized actions of dopamine and dopaminergic agonists is the stimulation of the site-selective phorphorylation of DARPP–32 (Fig. 2).[1] DARPP–32 is a cytosolic protein enriched in medium spiny neurons of the neostriatum and nucleus accumbens.[30] Through its actions on postsynaptic D–1 receptors, dopamine enhances the production of cAMP leading to the activation of PKA which in turn catalyzes the phosphorylation of DARPP–32 which converts this protein into a potent inhibitor of phosphoprotein phosphatase 1.[1] Recently,

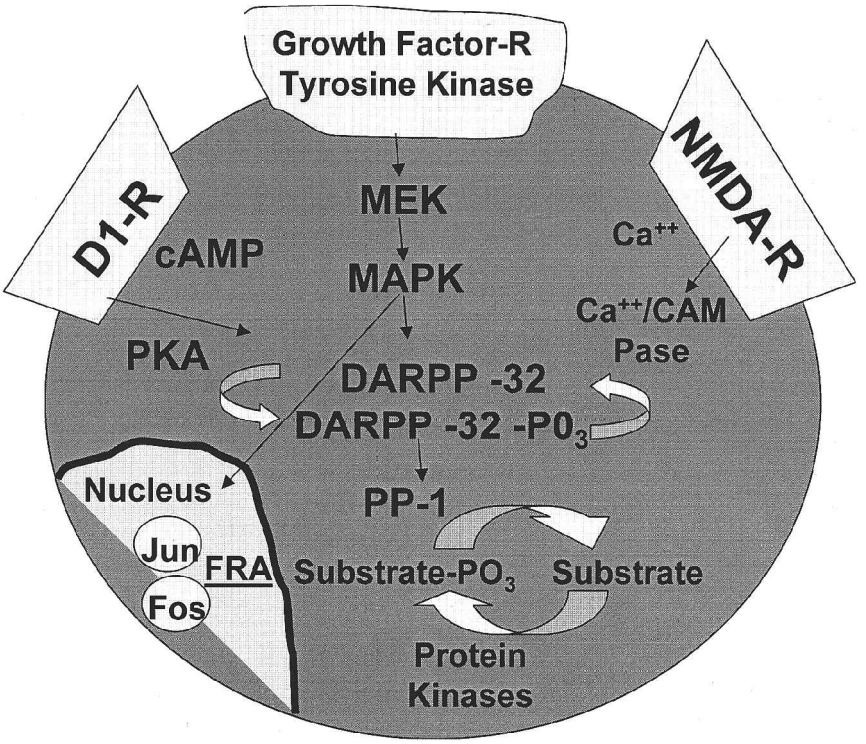

Figure 2. *Protein phosphorylation pathways in the basal ganglia involved in postsynaptic dopaminergic neurotransmission through the phosphatase inhibitor, DARPP–32. NMDA-R, NMDA receptor, D1-R, dopamine type 1 receptor, PKA, cAMP-dependent protein kinase; MEK, MAP kinase kinase; MAPK, mitogen activated protein kinase; DARPP–32, dopamine and cAMP-regulated phosphoprotein; FRA, fos-related antigens; PP–1, protein phosphatase–1; Pase, phosphatase; CAM, calmodulin. Figure adapted from Greengard* et al.[56]

mice lacking DARPP–32 were shown to have deficits in the molecular, cellular and behavioral responses to dopamine, drugs of abuse and antipsychotic agents,[31] findings indicative of the central role of DARPP–32 in dopaminergic neurotransmission.[31] In addition to dopamine, it is now known that several other neurotransmitters regulate the phosphorylation of DARPP–32, including transmitters implicated in the action of amphetamines,[32] such as glutamate. Moreover, DARPP–32 not only is acted upon by first and second messenger candidates, but itself regulates the phosphorylation and activation of specific neurotransmitter pathway receptors through its actions as an inhibitor of PP–1.[33]

A variety of amphetamines are believed to damage dopaminergic nerve terminals because they produce long-lasting (days to months) decrements in striatal dopamine and its metabolites,[34] decrements in the concentration of tyrosine hydroxylase and its catalytic activity,[35] reduced ligand binding to the dopamine transporter[36] and an induction of astrogliosis[8] and the silver degeneration reaction.[8] At first glance these neurotoxic actions of amphetamines would not appear to involve the DARPP–32 phosphorylation pathway because amphetamines target the presynaptic nerve terminal, not the DARPP–32 containing dopaminoceptic neurons of the neostriatum. However, evidence does exist implicating postsynaptic mechanisms in the presynaptic toxicity of amphetamines. For example, blockade of postsynaptic dopamine receptors has been reported to attenuate methamphetamine-induced damage to presynaptic dopaminergic nerve terminals in the rat neostriatum.[37,38] Furthermore, destruction of striatal neurons by local infusion of quinolinic acid, which results in loss of postsynaptic dopamine receptors[39] and DARPP–32[40] also attenuates dopaminergic nerve terminal damage following subsequent exposure to methamphetamine.[39]

The above observations suggested that dopaminoreceptive elements associated with intrinisic neurons of the neotriatum were involved in methamphetamine damage to dopaminergic nerve terminals in the neostriatum. To examine this possibility, we administered a neurotoxic regimen of methamphetamine[8] to wild-type mice and mice with targeted disruption of DARPP–32. The expected induction of striatal astrogliosis, as assessed by an assay for GFAP, and a decrease in dopamine, was observed in wild-type mice.[31] In contrast, mice lacking DARPP–32 showed a markedly attenuated response to methamphetamine as assessed by assays of GFAP and dopamine.[31] These data suggest that mice lacking DARPP–32 are less susceptible to methamphetamine-induced neurotoxicity compared to wild-type controls. Together with the data cited above, the findings of Fienberg and colleagues[31] implicate post-synaptic signaling pathways involving DARPP–32 in the underlying mechanisms of substituted amphetamine neurotoxicity. By inference, it is likely that inhibitors of protein phosphatase 1, in addition to DARPP–32, may play an important role in modulating amphetamine-induced dopaminergic neurotoxicity.

FRAs and dopaminergic neurotoxicity

While chronic stimulation of mesolimbic and nigrostriatal dopaminergic pathways by drugs of abuse can result in the prolonged expression of FRAs, so too can injury to the brain. Toxicant-, seizure-, and ischemia-induced neuronal cell death all are associated with increased AP–1 binding activity by fos and FRAs, including FRA–1 and FRA–2.[41–45] As with transcriptional activation associated with chronic dopaminergic signaling, FRA activation and subsequent AP–1 binding are associated with both phosphorylation of pre-existing factors and with induction of protein.[45] From a damage perspective, most FRA-linked increases in AP–1 binding have been associated with conditions that result in cell death,[44,45] with an enhanced expression of FRA occurring in neurons that survive brain injury, suggesting that FRAs are involved in enhancing transcription of genes related to the process of regeneration and repair.[44,45] A 35-kDa FRA, as well as FRA–2, are induced in hippocampal neurons after administration of the known hippocampal toxicants, kainate and trimethyltin;[42] (Pennypacker & O'Callaghan, unpublished results). The FRA-expressing cells have been identified as neurons, however a small population of GFAP-positive cells expressed FRA immunoreactivity after kainate-induced injury.[42] Little attention has been directed toward the possibility that non-lethal cellular injuries, such as nerve terminal degeneration, may elicit expression of FRAs as part of a repair or adaptive response to the insult. However, dopaminergic nerve terminal damage due to 6-hydroxydopamine has been shown to result in persistent elevation of FRA expression in dynorphinergic neurons[46] and the FRA involved has recently been identified as delta FosB.[47] Chronic administration of haloperidol also elevated FRAs, suggesting the effects of dopaminergic dennervation by 6-hydroxydopamine were the result of reduced postsynaptic receptor activation.[47] Unequivocal localization of FRA expression to neurons was not established in the latter study. In this regard, it is notable that in many studies of chronic FRAs, the onset, degree and duration of the FRA response to injury parallel the astroglial reaction to the insult. Additionally, both AP–1 transcription factor induction[44,45] and gliosis[48] have been implicated as participants in regenerative as well as degenerative response to toxicant-induced injuries.

FRA–2 and MPTP-, METH- and MDMA-induced neurotoxicity

As a first step toward determining the *in vivo* role of FRAs in brain injury responses where cell death is not a factor, we examined the potential of the known dopaminergic neurotoxicants, MPTP, METH and MDMA to induce the expression of FRA–2 in the striatum of C57Bl/6J mice.[49] The advantages of these injury models include: (1) a defined target of damage; (2) damage limited to dopaminergic nerve terminal degeneration; (3) known time course of gliosis; and (4) availability of pharmacological and physiological antagonists to manipulate neurotoxicity. Brain homogenates were analyzed for FRA–2 content (by quantitative immunoblots), gliosis (by GFAP ELISA) and dopamine (by HPLC). Representative FRA–2 immunoblots of striatal homogenates obtained from saline-, MPTP- and METH-treated mice are shown in Fig. 3. All three dopaminergic neurotoxicants caused large (three-fold) increases in striatal FRA–2 coincident with peak increases in GFAP and maximal decreases in dopamine; non-target regions were unaffected.[49] Increments

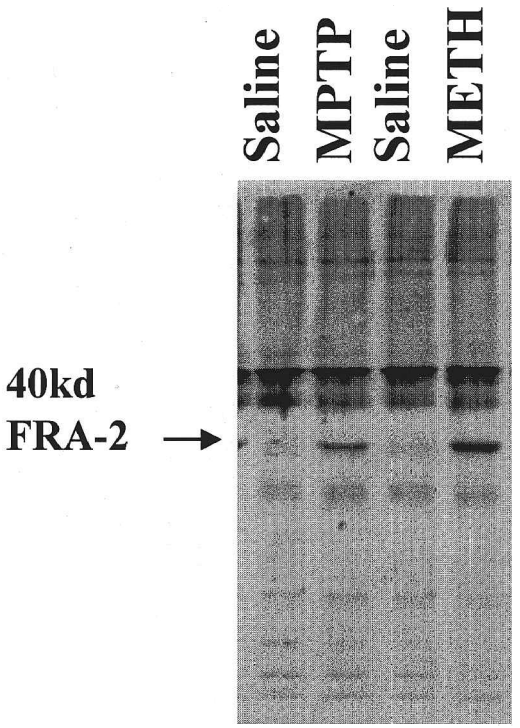

Figure 3. *Induction of FRA−2 in the mouse neostriatum 48 hours following administration of neurotoxic regimens of MPTP and methamphetamine.*

in FRA−2 and GFAP returned to control levels by 3-weeks post-dosing. Lowered ambient temperature, which blocks amphetamine but not MPTP-induced neurotoxicity, abolished METH but not MPTP-induced increases in FRA−2.[49] These data indicate that enhanced expression of FRA−2 coincides with nerve terminal degeneration induced by dopaminergic neurotoxicants that do not cause cell death.[8] The fact that as little as a single dose of these agents (MPTP) can cause terminal degeneration, gliosis and FRA induction stands in contrast to the requirement for chronic dosing with METH and cocaine for induction of FRAs in mesolimbic dopaminergic pathways.[3,4,5] Because the time−course for FRA induction by METH and MPTP coincides with the induction of gliosis, it is tempting to speculate that FRA−2 expression is localized to reactive astrocytes. Although enhanced gene expression certainly occurs in reactive astrocytes,[48] we have yet to define the localization of FRA−2 expression following the administration of METH or MPTP.

MAP kinase and dopaminergic neurotoxicity

One potential link between protein phosphorylation, activation of FRA−2, induction of gliosis and dopaminergic neurotoxicity is the MAP kinase pathway.

The MAP-kinase signaling module has been implicated as a downstream effector of growth-associated events.[50] These include phosphorylation of transcription factors, one of which is FRA−2.[51] Because brain injury results in phosphorylation of transcription factors[44,52] and the induction of reactive gliosis (a known growth associated event), we examined the potential for MAP kinase activation as a component of dopaminergic neurotoxicity.[53] Following the administration of MPTP, mice were sacrificed by focused microwave irradiation to preserve steady-state protein phosphorylation. Immunoblots of striatal homogenates were then probed with antibodies directed against the phospho-(active) form of p42/p44 MAP kinase. Phospho-(active) MAP kinase was found to be elevated by 50%, 3−6 hours post-MPTP.[53] These results are suggestive of a role of MAP kinase and potentially of MAP kinase-activated transcription factors in the early phase of injury-induced glial activation and/or damage to dopaminergic nerve terminals. As with data obtained for induction of FRA−2, the cellular localization of activated MAP kinase needs to be established. The participation of other kinase modules implicated in injury responses, such as the JAK-STAT pathway,[54] cannot be ruled out and they should also be examined in future investigations.

Conclusion

Injury to the CNS provokes a complex multicellular response in the affected region. Some of the targeted cells succumb to the insult whereas other react and adapt to the altered milleau.[44,45] We have shown that dopaminergic nerve terminal degeneration resulting from neurotoxic regimens of substituted amphetamines and MPTP elicits a rapid induction of the astrocyte protein, GFAP, the AP−1 transcription factor, FRA−2, and an activation of MAP kinase. This pattern of enhanced expression of specific proteins, as well as the activation of MAP kinase, resembles the molecular adaptation responses seen after drug-sensitizing regimens of amphetamine and cocaine. Moreover, postsynaptic dopaminergic signaling through the key effector phosphoprotein, DARPP−32, also appears to regulate the

psychostimulant and neurotoxic responses to amphetamines. At least with respect to the amphetamines, these observations suggest that some signaling pathways may be common to both the psychostimulant (addictive) and neurotoxic properties of these compounds. This does not imply that two very different actions of dopaminergic agonists, addiction and neurotoxicity, share the same underlying mechanism of action. Stimulation of dopamine receptors or damage to dopaminergic nerve terminals results in the enhanced expression of at least 30 genes.[55] Therefore, while the psychostimulant and neurotoxic actions of amphetamines may share some signaling pathways, it is likely that different (and complex) mechanisms are responsible for these different drug actions.[4,5] If effective pharmacotherapies are to be developed to prevent either of these adverse drug actions, the challenge remains to unravel the signaling pathways and molecular adaptations responsible for the addicted and neurotoxic condition.

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