particularly their utility for predicting climate responses to future forcings, including anthropogenic effects. Understanding the linkages could facilitate use of the solar cycle in seasonal climate predictions if the magnitudes of the effect are found to be sufficiently large. Knowing how solar variability has altered climate in the past may help constrain the magnitude of anthropogenic warming and internal variability over the past century. It also provides a first-order indication of what may be expected because of solar variability in the future compared with other climate forcings (see the graph, previous page). If substantial greenhouse gas reductions are achieved, projected solar forcing may counter a substantial fraction of the remaining anthropogenic forcing in the next few decades, providing unexpected complications for climate change detection when increasing certainty is expected and needed.

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PERSPECTIVES: NEUROSCIENCE

A Kinase to Dampen the Effects of Cocaine?

Amitabh Gupta and Li-Huei Tsai

Cyclin-dependent kinases (CDKs) are proteins that regulate the transition of cells from one phase of the cell cycle to the next (*1*). One surprising exception to this rule is Cdk5, which is not activated in dividing cells. Activity of Cdk5 is restricted to the central nervous system (CNS) and depends on Cdk5-specific activators, such as p35, which (in contrast to Cdk5) are expressed only in postmitotic neurons (*2, 3*). It is well established that Cdk5 is involved in both neurodevelopment and neurodegeneration. Exciting research from Paul Greengard's group now implicates Cdk5 in dampening down the neural changes in the CNS induced by chronic exposure to cocaine (*4*). The CNS usually adapts to chronic cocaine exposure by rendering the pathways that are stimulated by cocaine more resistant to the activity of this opiate. Greengard and colleagues show that Cdk5 is a crucial regulator of this adaptive response.

Mice deficient in the Cdk5 activator p35 are viable but suffer from an increased frequency of lethal seizures (*5*). Mice lacking Cdk5 have a more profound phenotype, dying shortly after birth (*6*). Histologically, both groups of knockout mice exhibit a layering defect in the neocortex of the brain that is believed to be caused by defective migration and adhesion of neurons during embryonic development (*7*). This neocortical phenotype resembles the phenotypes of *reeler* and *scrambler* mice, but is distinct from them in that the preplate (the first collection of migrating neurons to form a cortical layer) is split at embryonic day 13 (*7*). The severity of the phenotype in the Cdk5-deficient mice is linked to anatomical defects that extend beyond the neocortex to many areas of the CNS. Because these defects also arise from aberrant neuronal migration and adhesion, Cdk5 clearly is involved in regulating these processes in the developing CNS.

Cytoskeletal components, adhesion molecules, and signaling proteins can all mediate Cdk5 activity (*8–10*). Recently, Cdk5 was found to induce the abnormal phosphorylation of tau protein, which resulted in the concomitant degeneration of neurons in disorders such as Alzheimer's disease (*11*). Intriguingly, this effect was promoted by calpain-mediated cleavage of p35 into p25, which then aided in relocating and stabilizing Cdk5 (*12*). Thus, in addition to driving migration and adhesion events in neuronal development, Cdk5 facilitates neurodegenerative processes under neurotoxic conditions. The dual functions of Cdk5 rejuvenate the connection between neurodevelopment and neurodegeneration (*13*).

Cocaine increases the amount of the neurotransmitter dopamine in synapses by inhibiting the dopamine uptake transporter, which shuttles dopamine back into the nerve endings. In response to a greater supply of dopamine, dopamine-receptive neurons in the striatum become deregulated, resulting in the motor symptoms characteristic of chronic cocaine use. The deregulation of these neurons is accompanied by dopamine-induced activation of protein kinase A (PKA), which mediates the effects of cocaine by phosphorylating (adding phosphate groups to) a wide variety of proteins, including voltage-gated and ligand-gated ion channels (*14*).

A particularly important PKA target protein is DARPP-32, the dopamine and cyclic AMP regulated phosphoprotein (32 kD). Phosphorylation of amino acid threonine 34 by PKA allows DARPP-32 to bind to and inhibit the activity of protein phosphatase–1 (PP-1), which results in a diverse group of PP-1 target proteins remaining phosphorylated (activated) (see the figure, middle). Such targets include ion channels (some of which are also direct PKA targets) and transcription factors, for example, CREB (cAMP-responsive element binding protein). When phosphate groups are removed from Thr^{34} in DARPP-32 by several phosphatases—particularly by PP-2B (calcineurin)—the DARPP-32–mediated inhibition of PP-1 is blocked, counteracting the effects of PKA. Thus, DARPP-32 may be viewed as a "molecular switch" that balances the opposing effects of PKA and PP-2B in order to regulate and fine-tune the phosphorylation state of PP-1 target proteins (see the figure, middle). Notably, mice deficient in DARPP-32 have increased motor sensitization to chronic cocaine administration (*15*). This finding suggests that the PKA–DARPP-32–PP-1 axis is likely to dampen the effects of chronic cocaine exposure, which stands in contrast to many

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other signaling events downstream of PKA that result in potentiation of chronic cocaine effects (see the figure, left).

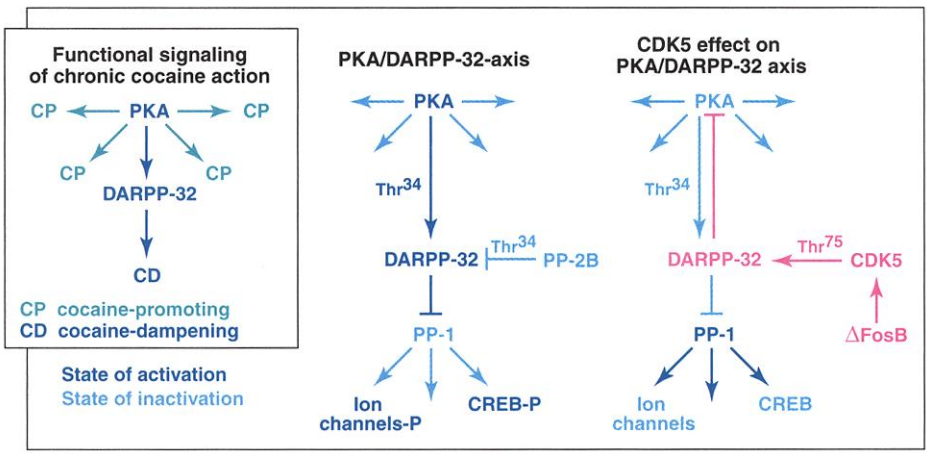
Previous work from Greengard's group demonstrated that Cdk5 phosphorylates DARPP-32 at threonine 75 (Thr^{75}), thus squarely planting Cdk5 in the dopamine signaling pathway (*16*). Interestingly, once Thr^{75} is phosphorylated, DARPP-32 cannot be phosphorylated at Thr^{34} by PKA, and so loses its ability to inhibit PP-1. More important, DARPP-32 phosphorylated at Thr^{75} is a strong inhibitor of PKA, resulting in the reduced phosphorylation of PKA-dependent target proteins (see the figure, right). Consistent with this finding, mice deficient in p35 have decreased amounts of phospho-Thr^{75} DARPP-32 and increased phosphorylation of PKA-dependent targets. The Greengard group concluded that Thr^{75} phosphorylation by Cdk5 transforms DARPP-32 from a PP-1 inhibitor into a PKA inhibitor (*16*).

In their new work, Greengard and colleagues unravel how Cdk5 modulates the effects of chronic cocaine in the striatum (*4*). The authors detect increased expression of Cdk5 and p35 both in rats administered cocaine chronically and in mice that overexpress the transcription factor ΔFosB (which is elevated in striatal neurons in response to chronic cocaine). Interestingly, Nestler's group (*17*) has independently reported elevation of Cdk5 in the hippocampus (but not in the striatum) of ΔFosB transgenic mice induced to have seizures. Taken together, these findings identify the genes encoding Cdk5 and p35 as targets of ΔFosB transcriptional activity. Next, Greengard and co-workers report increased phosphorylation of DARPP-32 at Thr^{75} and decreased phosphorylation of PKA-dependent target proteins in both the rat and mouse models. Consistent with the ability of phospho-Thr^{75} DARPP-32 to inhibit PKA activity, pharmacological inhibition of Cdk5 in both animal models rescues PKA-dependent phosphorylation of DARPP-32 at Thr^{34} and restores phosphorylation of other PKA-dependent targets. Finally, inhibition of Cdk5 potentiates the locomotor effects of chronic cocaine in mice and rats.

At first glance, this behavioral response may come as a surprise, given that Cdk5 blocks the PKA–DARPP-32–PP-1 axis, which by itself has a dampening effect on cocaine's action. Hence, inhibition of Cdk5 would be expected to disinhibit this PKA axis and to result in restriction, not potentiation, of chronic cocaine action (see the figure, right). However, as Cdk5 broadly reduces PKA activity, blocking Cdk5 will also disinhibit the many PKA-dependent pathways that by themselves are cocaine-promoting (see the figure, left). Thus, the net effect of Cdk5 inhibition is actually a potentiation of the effects of chronic cocaine in striatal neurons.

These exciting results provide a glimpse of the intricate molecular pathways in the brain that are altered by chronic cocaine exposure. But some aspects of these molecular pathways remain controversial. For example, ΔFosB induction may actually contribute to a state of cocaine addiction, because ΔFosB transgenic mice have a marked predilection for cocaine in some studies (*18*). This result would fit with the Greengard data, if most of the ΔFosB-induced genes turn out to be of a cocaine-promoting nature. As signaling connections between DARPP-32–regulated CREB and ΔFosB emerge, they pose the question of how to resolve the discrepancy between the possible cocaine-promoting activity of ΔFosB and the cocaine-dampening effects of DARPP-32. In light of such a discrepancy, we are reminded that signaling networks are finely tuned interconnected systems, with intricate positive and negative feedback loops. Future research will certainly resolve such discrepancies by unveiling more of the intricacies of cocaine signaling.

Are there further links between Cdk5 and chronic cocaine effects that remain to be discovered? Conceivably, there are additional Cdk5 targets in the dopamine signaling pathway. The localization of PP-1 to the dendritic spines of neurons, for example, is thought to depend on the protein spinophilin (*14*). Interestingly, spinophilin localizes to sites where cells adhere to each other through N-cadherin (*19*). Considering that Cdk5 is involved in cadherin-based neuronal adhesion (*10*), it may regulate the subcellular localization of the PP-1–spinophilin complex. Alternatively, Cdk5 may affect dopamine signaling by regulating PP-1 enzyme activity through modulation of inhibitor-1, a potent PP-1 blocker. Evidence to support such a notion comes from the finding that Cdk5 can phosphorylate inhibitor-1 at Ser^{67} (*20*). Future research should extend our understanding of the part played by Cdk5 in the long-term effects of chronic cocaine exposure on the CNS. In light of exciting recent progress in the field, we should not have too long to wait.



Signaling the effects of cocaine. (Left) Whereas various PKA-dependent signaling pathways promote the effects of chronic cocaine (green), the PKA–DARPP-32 axis dampens these effects (blue). **(Middle and Right)** The activation and inactivation of signaling molecules are marked by dark and light shading, respectively. **(Middle)** Molecular interactions within the PKA–DARPP-32 signaling axis. PKA activates DARPP-32 by phosphorylating residue Thr^{34}; phospho-Thr^{34} DARPP-32 then binds to and inhibits PP-1, which maintains PP-1 target proteins in a phosphorylated, activated state. In contrast, PP-2B inhibits DARPP-32 activity by dephosphorylating Thr^{34}. **(Right)** Cdk5 inhibits the PKA–DARPP-32 signaling axis. Cdk5 is induced by the transcription factor ΔFosB and phosphorylates DARPP-32 on Thr^{75}. Phospho-Thr^{75} DARPP-32 not only becomes unresponsive to phosphorylation by PKA, but also directly inhibits PKA activity. Consequently, PP-1 is disinhibited and PP-1 targets are dephosphorylated and inactivated.

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