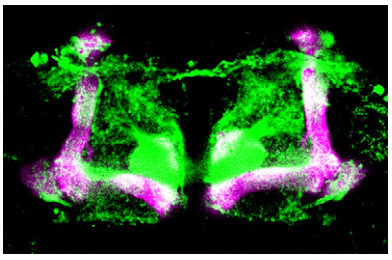
# Neurobiology Select

Cell

The dopaminergic neurons of the central nervous system regulate behavior associated with reward and punishment. Loss of dopamine neurons in the substantia nigra leads to Parkinson's disease. This issue's Neurobiology Select discusses the discovery of a neural circuit involved in decision making in flies and a report showing that associative learning shifts the timing of dopamine signaling in rodents. Other new work identifies molecular pathways that modulate neuronal death in models of Parkinson's disease suggesting new therapeutic approaches, including returning mature dopamine neurons to a youthful pattern of neuronal firing.

## Making Decisions on the Fly

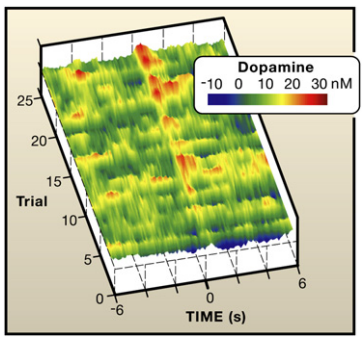


Immunostaining of the fly brain shows both the dopamine system (green) and the mushroom body (magenta). Image courtesy of K. Zhang.

How does one make a choice when the outcome is uncertain because of conflicting information? Insight into this vexing problem comes from recent work by Zhang et al. (2007). They report the identification of a neural circuit in the fruit fly *Drosophila* involved in making value-based decisions. Using a flight simulator, they trained flies to associate a colored bar at a particular location in its visual field with a punishment, in this case, heat. Having learned this task, the authors then observed how the flies would behave if presented with conflicting cues (for instance, a bar in the right place but the wrong color, or bars with different positions and different intensities). They found that wild-type flies had strong and distinctive responses to these dilemmas, whereas mutant flies that had a smaller brain region called the mushroom body were less choosy in their behavior, even though they were equally capable of learning the initial training task. The investigators further characterized the neural circuitry underlying this effect by expressing a temperature-sensitive mutant of the GTPase dynamin in specific neuronal populations to block neuronal function. These efforts revealed that disruption of dopaminergic neurons had a similar effect on fly behavior as disruption of mushroom body neurons in these decision-making tasks, suggesting that the two pathways may be connected. Indeed, immunostaining shows that dopaminergic neurons extensively innervate the mushroom body (see figure). Future work may establish how these connections are modified by learning and how they mediate decision making.

*K. Zhang et al. (2007). Science* ***316****, 1901-1904*.

## Going from Appreciating to Expecting a Reward




A reward-predictive stimulus (onset at time 0) evokes dopamine release in the nucleus accumbens that emerges as conditioning progresses. Data courtesy of R. Carelli.

Previous work has proposed that the innervation of the nucleus accumbens in the brain by midbrain dopamine neurons provides instructive information enabling prediction of whether a given stimuli will result in a rewarding outcome. Day et al. (2007) now report the dynamics of dopamine release at high temporal resolution in the nucleus accumbens in rats learning to associate a stimulus with a reward. In the learning paradigm used by the authors, rats were trained to associate the extension of a lever and a light cue with the delivery 10 s later of a sucrose pellet. Dopamine release was monitored directly by electrochemical recording from precisely positioned electrodes. Early during conditioning, before the association between the stimuli and reward had been established, dopamine release peaked when animals obtained a reward. However, later during training, this pattern shifted such that the peak in dopamine release came at the time of the presentation of the predictive stimulus and not the reward. Thus the timing of the reward signal provided by dopamine is dynamically regulated by associative learning.

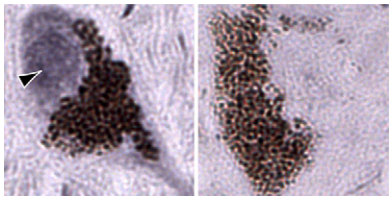
*J.J. Day et al. (2007). Nat. Neurosci. Published online July 1, 2007. 10.1038/nn1923.*

## A New Defender Rallies Dopamine Neurons under Siege

Searching for new factors that might stall the neurodegeneration in Parkinson's disease, Lindholm et al. (2007) now report the discovery of CDNF (conserved dopamine neurotrophic factor). CDNF was identified based on its homology to another recently characterized protein MANF (mesencephalic astrocyte-derived neurotrophic factor). The authors tested the ability of CDNF to promote neuronal survival in a rat model of Parkinson's disease. In this model, neurodegeneration is triggered by intrastiatal injection of the neurotoxin 6-OHDA, which selectively kills dopaminergic neurons. Their results show that CDNF promotes neuronal survival, even when it is administered 4 weeks after

6-OHDA injection. This finding is similar to that previously shown for glial cell line-derived neurotrophic factor (GDNF), which reached phase II clinical trials in Parkinson's patients. Future work may establish how CDNF mediates its neuroprotective and neurorestorative effects. In this regard, the finding that CDNF has orthologues in invertebrates might prove advantageous for the rapid discovery of cellular pathways activated downstream of CDNF.
*P. Lindholm et al. (2007). Nature **448**, 73–77.*

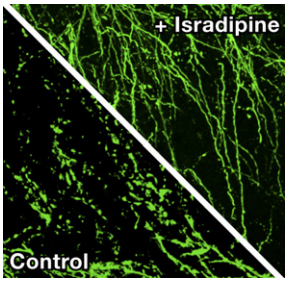
## A Protective Peroxidase



**Prx2 phosphorylation (arrowhead shows black soma staining) is upregulated in the dopamine nigral neurons (punctate brown neuromelanin) of Parkinson's disease patients (left) compared to age-matched control patients (right). Image courtesy of M. Mount.**

Previous work has shown that activation of the kinase Cdk5/p35 is a central mediator of the neurotoxicity caused by MPTP, a neurotoxin that triggers symptoms of Parkinson's disease in rodents and humans. MPTP induces mitochondrial dysfunction, which triggers altered $Ca^{2+}$ regulation and enhanced oxidative stress. In their current work, Qu et al. (2007) identify a critical substrate of Cdk5/p35 that mediates MPTP toxicity. This substrate is Prx2, a peroxidase enzyme that eliminates reactive oxygen species. Phosphorylation of Prx2 by Cdk5 decreases its enzymatic activity, and consequently neurons lacking Cdk5/p35 are shown to have reduced levels of reactive oxygen species. Thus, the authors propose a sequence of events that occur as a consequence of MPTP treatment: an increase in $Ca^{2+}$ elevates calpain protease activity leading to Cdk5 activation and Prx2 phosphorylation, which contributes to an increase in reactive oxygen species and enhanced neuronal cell death. The authors also observe elevated Prx2 phosphorylation in postmortem samples from Parkinson's patients indicating that a reduction in activity of this peroxidase is likely a characteristic feature of Parkinson's disease in humans (see figure). These findings suggest that enhancing Prx2 activity may be a new strategy for the treatment of Parkinson's disease.
*D. Qu et al. (2007). Neuron **55**, 37–52.*

## Sometimes Juvenile Behavior Should Be Encouraged




**Blocking the $Ca_v1.3$ channel with isradipine (right) protects dendrites of dopaminergic neurons (green) against rotenone, as compared to an unprotected control (left). Image courtesy of C.S. Chan.**

Why are the dopaminergic neurons of the substantia nigra particularly susceptible to degeneration and death? The answer according to Chan et al. (2007) might be related to their reliance upon $Ca^{2+}$ channels to support an intrinsic pattern of rhythmic firing called pacemaking. These authors show that the mechanism by which pacemaking of dopaminergic neurons of the substantia nigra is maintained changes during development, becoming increasingly reliant on the L type $Ca_v1.3$ $Ca^{2+}$ channels as the neurons mature. Yet, remarkably, adult mice lacking expression of $Ca_v1.3$ $Ca^{2+}$ channels retain pacemaking in these dopaminergic neurons through a mechanism that resembles pacemaking in juvenile animals, which is dependent upon $Na^+$ channels. Even more surprising, the authors then demonstrate that this juvenile form of pacemaking can be reactivated in adult neurons of wild-type animals following the administration of isradipine, a $Ca_v1.3$ $Ca^{2+}$ channel blocker. It has been suggested that excess $Ca^{2+}$ might be involved in the neurotoxicity of Parkinson's disease. The authors reasoned that eliminating the dependence of adult neurons on $Ca^{2+}$ for pacemaking might protect them from insults that lead to neuronal death. They tested this hypothesis and showed that reversion to the juvenile mechanism of pacemaking (which they call rejuvenation) does indeed protect dopaminergic neurons of the substantia nigra from three different toxins—rotenone, 6-OHDA, and MPTP—that render rodents and primates parkinsonian (see figure). The $Ca_v1.3$ $Ca^{2+}$ channel blocker, isradipine, is already in clinical use for the treatment of high blood pressure. Future clinical trials combined with analysis of those currently taking the medication may establish whether isradipine slows the onset and progression of Parkinson's disease.
*C. S. Chan et al. (2007) Nature **447**, 1081–1086. Published online June 10, 2007. 10.1038/nature05865.*

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