occurs in response to chronically low blood flow, was blocked in the $P2X_4$ receptor–deficient mice.

As these findings provide insight into the molecular mechanisms underlying vascular tone and remodeling, the authors speculate that this report may help develop new therapies for blood pressure disorders. Unfortunately, selective agonists and antagonists for the $P2X_4$ receptors are not yet available. ATPγS is a potent but not selective $P2X_4$ agonist, whereas the nonspecific P2 receptor antagonists suramin, pyridoxal phosphate-6-azophenyl-2', 4'-disulphonic acid and Reactive blue 2 do not inhibit $P2X_4$ receptor–mediated responses; indeed they potentiate the ATP response by inhibiting ectonucleotidases[4]. The wide variation in vascular control by purines and pyrimidines must also be recognized; further investigation is needed to establish which vessels in which species use $P2X_4$ receptors as the principal endothelial P2 receptor subtype mediating release of nitric oxide.

The importance of purinergic signaling in cardiovascular diseases[12] is highlighted by the recent use of $P2Y_{12}$ receptor antagonists, like clopidogrel, for the treatment of thrombosis and stroke—by the use of P1 receptor agonists, such as adenosine, for treatment of supraventricular tachycardia (rapid heart rate originating in the lower heart chambers).

Although considerable effort has been expended to produce selective agonists and antagonists for P1 and P2 receptor subtypes[13], drugs that target the different subtypes, including the $P2X_4$ receptor, and that are not degraded *in vivo*, are still awaited.

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A channel to neurodegeneration

Ariel Y Deutch & Danny G Winder

In people with Parkinson disease, neurons in certain brain regions are more likely to die than others. A potassium channel may be the key to understanding this differential neuronal death.

Neurodegenerative disorders are bigots. None attack all brain cells, and many discretely target neurons in only a few areas. Why there is a loss of midbrain dopamine neurons that are next to ones spared in Parkinson disease is intensely studied. In a surprising twist on the usual suspects, a study in the December issue of *Nature Neuroscience* may explain the differential vulnerability of dopamine cells in Parkinson disease[1].

In Parkinson disease, dysfunction of the mitochondrial electron transport chain, increases in reactive oxygen species, and decreases in ATP production contribute to dopamine cell death in the substantia nigra[2], a region in the midbrain. The dopamine neurons of the substantia nigra, and the striatal dopamine innervation derived from these neurons, undergo a selective (or regionally specific) pattern of degeneration in Parkinson disease. Symptoms arise when dopamine axons in the striatum are lost. In contrast, the dopamine neurons in an adjacent midbrain region, the ventral tegmental area, are much less affected.

What governs the differential loss of midbrain dopamine neurons in Parkinson disease remains a source of speculation. Potential explanations include differing degrees of expression of the dopamine transporter (through which xenobiotics access dopamine neurons), the presence or absence of the calcium binding protein calbindin, and variations in molecules that counter oxidative stress[4,5]. But none of these explanations has proven completely satisfactory.

Liss *et al.* now provide evidence that ATP-sensitive potassium (K_{ATP}) channels may help determine the selective loss of substantia nigra, but not ventral tegmental area, dopamine cells in Parkinson disease[1]. K_{ATP} channels are metabolic sensors that couple cellular energy metabolism to membrane potential by regulating potassium flux. In the midbrain dopamine neurons, the K_{ATP} channels are composed of a pore-forming inward-rectifying potassium channel subunit known as Kir6.2 and a regulatory sulfonylurea receptor subunit known as Sur1. Sulfonylureas are drugs used in the treatment of type 2 diabetes that close K_{ATP} channels and densely bind neurons of the substantia nigra.

Liss *et al.* reported that the mRNA encoding K_{ATP} channels comprising Kir6.2 and Sur1 are abundantly expressed in substantia nigra dopamine neurons. They found that metabolic challenges with parkinsonism-inducing toxins, such as MPTP, cause rapid hyperpolarization and electrical 'silencing' of dopamine cells in the substantia nigra, but not in the ventral tegmental area. In contrast, nigral dopamine neurons from Kir6.2 knockout mice were not hyperpolarized with these toxins.

MPTP treatment of mice causes extensive loss of substantia nigra dopamine neurons and the dopamine innervation of the striatum[6]; in contrast, Liss *et al.* found that Kir6.2 knockout mice are relatively resistant to MPTP. When *weaver* mice— which suffer a developmentally specific loss of substantia nigra neurons[7]—were crossed with Kir6.2 null mice, the absence of K_{ATP} channels attenuated the loss of substantia nigra dopamine neurons in these mice. These studies suggest that the K_{ATP} channel may help determine whether a dopamine neuron

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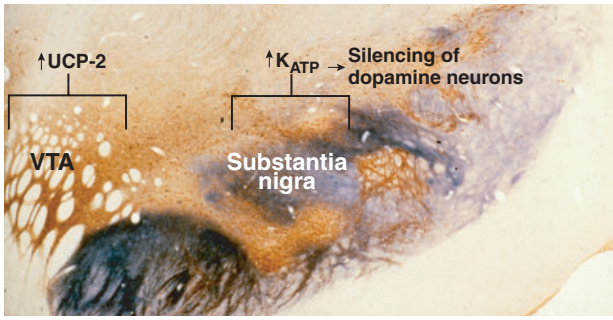

Figure 1 In Parkinson disease, only certain dopamine neurons in adjacent regions of the midbrain are lost; Liss *et al.* report a potential explanation. High expression of K_{ATP} channels in the dopamine neurons of the substantia nigra may trigger preferential cell death. On the other hand, lower expression of this channel and higher expression of the uncoupling protein UCP-2 in dopamine neurons of the ventral tegmental area (VTA) may block neuron loss.

lives or dies. The work may also open the door for new therapeutic strategies aimed at slowing the progression of Parkinson disease.

If K_{ATP} channels govern differential vulnerability of dopamine neurons in Parkinson disease, it would provide a mechanism for the coupling of metabolic disturbances in dopamine neurons with functional effects on membrane potential and cell firing. The K_{ATP} channel, however, is downstream of the metabolic perturbations. Accordingly, the pathological process involving dopamine neurons must occur before K_{ATP} channel–induced silencing of dopamine neurons. Therefore, it is likely that K_{ATP} channels are not the sole mediators of degeneration in dopamine neurons.

Interestingly, Liss *et al.* noted that ventral tegmental area dopamine neurons express higher levels of uncoupling protein UCP-2 than do vulnerable substantia nigra neurons, and mild mitochondrial uncoupling decreases K_{ATP} channel function. This suggests that UCP-2 may be upstream of K_{ATP} in determining vulnerability of dopamine neurons (**Fig. 1**). Another recent study reported that UCP-2 knockout mice show increased MPTP-induced neuronal death[8].

A major question now is how K_{ATP} channel–mediated silencing of dopamine neurons triggers cell death. This finding runs counter to prevailing notions that neurodegeneration is associated with hyper- rather than hypoexcitability. One could envision that K_{ATP}-induced silencing of dopamine neuron activity ultimately works through a series of interconnected brain regions, which may also underlie the therapeutic effects of deep brain stimulation in Parkinson disease. Alternatively, decreased membrane excitability and firing rate of dopamine neurons may disrupt autaptic trophic support (self-produced growth factors). Regardless of the downstream mechanism, the work of Liss *et al.* suggests that neuronal silence may not always be golden.

Individuals with Parkinson disease also have an impaired insulin response to glucose[9]. Sulfonylurea drugs, which are used to treat type II diabetes, block K_{ATP} channels. The findings of Liss *et al.* suggest that such drugs may be useful in the treatment of Parkinson disease and may reduce the risk, or slow the progression, of the illness. We are unaware of any epidemiological studies that report an association between Sur1 or Kir6.2 and Parkinson disease; such a study is warranted.

Clinical trials in parkinsonism with tolbutamide—a sulfonylurea drug—conducted before the modern era of therapies for Parkinson disease were inconclusive[10]. The data hinted, however, that this drug may be effective in less severely affected individuals with Parkinson disease. If dopamine neurons have not yet degenerated, perhaps K_{ATP} channel antagonists could slow disease progression.

The work of Liss *et al.* provides sorely needed new targets for slowing the progressive loss of dopamine neurons in Parkinson disease. Perhaps the new targets will allow us to reach a point where all dopamine neurons are left behind.

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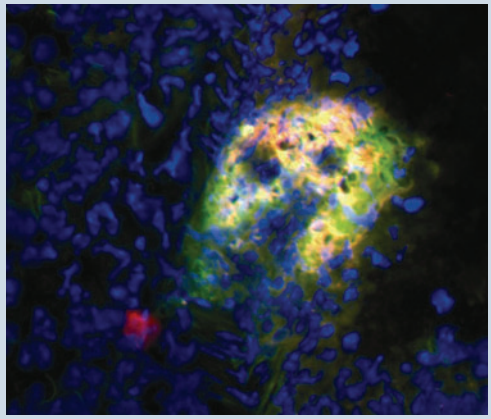
Envoys of metastasis



Bone marrow cells lodged throughout the body seed the development of metastases in mice, report Rosandra Kaplan and colleagues (*Nature* **438**, 820–827). What's more, blocking a signal from the marrow cells can prevent the migration of metastatic cells to these locations.

The researchers first observed that bone marrow cells clustered at pre-metastatic locations before the arrival of tumor cells. These progenitor bone marrow cells were identified using markers typical of such cells. The cells also expressed vascular endothelial growth factor receptor-1 (VEGFR1), which seemed to be necessary for migration of metastatic cells. Shown is one such cluster of marrow cells (VEGFR1 in red, GFP-labeled marrow cell in green and DNA in blue).

It is unclear what causes the bone marrow cells to cluster in the first place. But in mice with tumors, expression of a protein that sticks to bone marrow cells, fibronectin, was somehow increased at organs that conventionally host metastatic tumors.

To show the involvement of VEGFR1, the researchers grew tumor cells in the presence of VEGFR1-expressing cells; as a result, the tumor cells adhered more strongly and divided more rapidly. VEGFR1 cells isolated from pre-metastatic clusters secreted growth factors, which may attract circulating tumor cells.

Finally, antibodies that blocked VEGFR1 completely prevented metastases in animals with established tumors. To date VEGF inhibitors have been used in clinical trials with the aim of thwarting angiogenesis and tumor blood supply. The findings suggest that they might be of use to block metastasis.

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