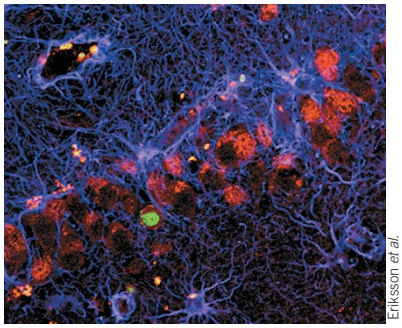
Stroke of fortune

The clot-busting drug tissue plasminogen activator (tPA) remains the only FDA-approved treatment for stroke. Although it has been in clinical use since the 1980s, it was not until 1995 that the first randomized, placebo-controlled study using recombinant tPA in stroke patients was published. In this study, researchers at the National Institute of Neurological Disorders and Stroke (*N. Engl. J. Med.* **333**, 1581–1587) showed that patients treated with tPA were 30% more likely than placebo-treated patients to have zero to minimal disability three months later. Although this was the first treatment to improve outcome after stroke, tPA was also found to increase the likelihood of cerebral hemorrhage, a problem still being tackled by physicians and researchers a decade later. Later studies showed that tPA also promotes excitotoxic and ischemic injury within the brain and exacerbates neurodegeneration. Despite an ongoing search for better stroke therapies, none so far have measured up to the clinical efficacy of tPA. —*SG*

Source of cells



Eriksson *et al.*

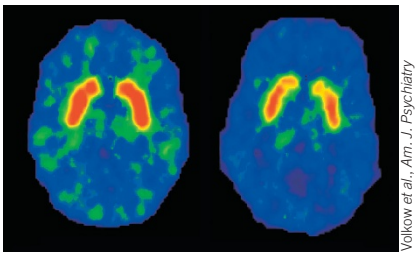
A new neuron labeled with BRDU (green) in the human brain.

Anyone who took an introductory neuroscience course before 1998 was sure to have been told that human brain cells cannot be replaced. But as early as 1965 this dogma was beginning to be questioned. Then, Joseph Altman and Gopal Das showed that neurogenesis occurs in the mature brain of the rat and guinea pig (*Nature* **214**, 1098–1101; 1965; *J. Comp. Neurol.* **124**, 319–335; 1965).

In the late 1990s, the dogma dissolved. In 1998, Elizabeth Gould *et al.* observed neurogenesis in adult monkeys (*Proc Natl Acad Sci USA* **95**, 3168-71). And later that year Peter Eriksson *et al.* showed, in *Nature Medicine* (**4**,1313–1317), that the human adult hippocampus also undergoes neurogenesis. In this study, the investigators infused cancer patients with 5-bromo-2-deoxyuridine (BrdU), which was incorporated into dividing cells for diagnostic purposes. Postmortem brain tissue from these patients provided unmistakable evidence that neurons had in fact divided, as the BrdU immunoreactive product was clearly seen in brain cells. This work was quickly followed by a 1999 study in *Cell* (**97**, 703–716) by Fiona Doetsch *et al.*, showing that astrocytes in the subventricular zone, the area around the ventricles, are the precursors of the new neurons in the adult brain. Another source of new neurons was later found in a region of the hippocampus, the dentate gyrus subgranular zone. These studies revolutionized thinking about the central nervous system and injury, gave the term 'neuroplasticity' new meaning and opened the door to potential therapies to stimulate the brain's endogenous capacity for regeneration. —*SG*

Written by Stacie Grossman and Juan Carlos López in consultation with experts in the field.

What you crave



Volkow *et al.*, *Am. J. Psychiatry*

The brain of a subject who reports displeasure in response to methylphenidate (left) has more dopamine receptors than a subject with pleasurable feelings (right).

The role of dopamine in addiction has been the subject of intense investigation over the past decade. Several studies in the late 1990s were crucial to defining the contribution of this neurotransmitter and its receptors to cocaine addiction and craving.

In 1997, Nora Volkow *et al.* (*Nature* **386**, 830–833) used brain-imaging techniques to show that in drug addicts dopamine release was reduced in the striatum, an area of the brain's reward system. The results challenged the prevailing view that addiction was associated with increased dopamine release. In the same study, the researchers found that dopamine release in the thalamus—a relay station of sensory information to the cerebral cortex—was unexpectedly increased during drug craving, moving the focus of attention away from the striatum. In this study, the action of dopamine seemed to take place through its D_2 receptor subtype.

Two years later, Volkow *et al.* (*Am. J. Psychiatry* **156**, 1440–1443; 1999) took a closer look at the D_2 receptor. They found that the abundance of this receptor predicted the response to psychostimulants: people with fewer D_2 receptors reported more pleasant feelings in response to a drug than people with a higher receptor number. Volkow *et al.* pointed to the absence of this receptor subtype as a risk factor for addiction, eroding previous notions that high levels of the D_2 receptor predispose to addiction.

In the meantime, others were working on the contribution of additional dopamine receptor subtypes. In 1999, Maria Pilla *et al.* (*Nature* **400**, 371–375) designed the first dopamine agonist selective for the D_3 receptor subtype. The researchers showed that this agonist selectively inhibited cocaine-seeking behavior; it did not affect motor performance or drug intake *per se*, nor have any intrinsic rewarding effects. Phase 1 clinical trials for the agonist—BP 897—are underway for the management of drug abuse. —*JCL*

In it for the long haul

Addiction has long been thought to require long-lasting changes in neuronal physiology. Several studies published in the mid-1990s gave strong support to this idea, and one of them specifically provided the first molecular handle on the problem.

In 1994, Bruce Hope *et al.* (*Neuron* **13**, 1235–1244) found that the transcription factor known as the activator protein-1 complex, which consists of Jun and Fos-like proteins, undergoes long-lasting changes in response to repeated drug administration. These changes lasted longer than a week, and provided the first glimpse of how drug-induced molecular events could lead to the development of addiction—an idea that has been subsequently reinforced by countless studies and expanded to include other transcription factors.

The overarching idea is that drugs of abuse have long-lasting effects on the transcription of genes, the products of which modify neuronal structure and function, ultimately leading to addictive behavior. Although the effector mechanisms that act downstream of transcription are not completely understood, this concept has profoundly influenced thinking about the neural basis of drug dependence. —*JCL*