in the nucleus accumbens, a major VTA target and another key reward component, reversed the suppressive effect of BDNF on morphine reward.

Downstream from BDNF, the team found that several genes were involved in mediating its effects. Reducing the expression of the transcription factor Sox11 in the nucleus accumbens increased CPP, and overexpressing the immediate early gene *Gadd45g* in the same brain region further enhanced the effect of morphine.

This very thorough study indicates that BDNF has a nuanced role in the brain's response to drugs of abuse, as the opposite effect—a strengthened effect of cocaine after BDNF administration—had previously been reported. The cellular specificity and downstream mechanisms that account for these different effects have yet to be fully elucidated.—JCL

■ AUTOIMMUNITY

IL-26: inducing inflammation

A recent study identifies the interleukin-10 (IL-10) cytokine family member IL-26 as a key upstream mediator of the inflammatory cascade in rheumatoid arthritis (*PLoS Biol.* 10, e1001395).

IL-26 has previously been shown to be overexpressed in Crohn's disease, which suggests that it may be involved in the pathogenesis of chronic inflammatory disorders. Murielle Corvaisier *et al.* investigated this cytokine in human rheumatoid arthritis and found that it is overexpressed in the serum and synovial fluid from patients with rheumatoid arthritis compared with healthy subjects. IL-26 was constitutively expressed by the synovial cells in rheumatoid arthritis joints, and its production was upregulated by IL-1 β and IL-17A, both of which are known to be involved in rheumatoid arthritis pathogenesis.

The authors then found that IL-26 induced the expression of proinflammatory cytokines and chemokines by cultured myeloid cells. As rheumatoid arthritis is characterized by T helper type 1 (T_H1) and T_H17 inflammatory responses, they then investigated whether IL-26 can influence the type of T_H response induced. Using coculture experiments, the authors found that, via secretion of IL-1 β , IL-26-treated monocytes can induce the polarization of memory CD4⁺ T cells into T_H17 cells.

The authors suggest that IL-26 could be a potential therapeutic target in rheumatoid arthritis and that its role should also be investigated in other inflammatory disorders.—MS

■ CARDIOVASCULAR DISEASES

Degradation relieves the pressure

Drugs that activate the nuclear hormone receptor peroxisome proliferator-activated receptor γ (PPAR- γ) lower blood pressure, whereas dominant-negative mutations in the gene encoding PPAR- γ cause hypertension. Helping to explain these effects, Christopher Pelham *et al.* uncover a new mechanism by which PPAR- γ controls vasoconstriction and blood pressure (*Cell Metab.* 16, 462–472).

Véronique Estiot / Science Source

Using mice expressing a dominant-negative mutant version of PPAR- γ in smooth muscle cells, the researchers identified the protein RhoBTB1 as a direct transcriptional target of PPAR- γ in vascular smooth muscle. RhoBTB1 binds cullin-3, a ubiquitin ligase component, and cullin-3 in turn is known to promote the degradation of the small GTPase RhoA, a key regulator of vasoconstriction. In accord with this proposed pathway, the PPAR- γ -mutant mice had reduced amounts of vascular RhoBTB1, cullin-3 and RhoA proteins. This pathway seems to be responsible for the increased blood pressure in the mutant mice: for example, treatment of wild-type mice with an inhibitor of cullin-3 function raised both vascular RhoA protein amounts and blood pressure, but the inhibitor did not further increase blood pressure in the PPAR- γ -mutant mice.

The antihypertensive function of cullin-3 uncovered in this study may also shed light on the recent discovery that mutations in the gene encoding cullin-3 cause hypertension in humans.—MB

Written by Michael Basson, Alison Farrell, Juan Carlos López, Carolina Pola and Meera Swami

New from NPG

Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation

Landsberg, J. *et al. Nature* doi:10.1038/nature11538 (10 October).

A new study provides mechanistic insights into how tumors can acquire resistance to adoptive cell cytotoxic T cell therapy. The authors show that in a mouse melanoma model, resistance occurs through the reversible loss of melanocytic antigens on melanoma cells, which is triggered by inflammation. They identify the proinflammatory cytokine tumor necrosis factor- α as a key factor that induces this dedifferentiation of the melanoma cells.

De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia

Xu, B. *et al. Nat. Genet.* doi:10.1038/ng.2446 (3 October).

By sequencing the exomes of individuals with schizophrenia and of their unaffected parents, the authors find that the individuals with schizophrenia have a greater number of *de novo* mutations that cause protein-coding changes than would be expected. In addition, they identify four candidate genes that have recurrent alterations in individuals with schizophrenia.

The kinase TBK1 controls IgA class switching by negatively regulating noncanonical NF- κ B signalling

Jin, J. *et al. Nat. Immunol.* doi:10.1038/ni.2423 (30 September).

The authors identify the B cell regulatory molecule TBK1 as a key regulator of antibody class switching to immunoglobulin A (IgA). They show that mice lacking TBK1 expression in their B cells produce higher serum amounts of IgA and autoantibodies and develop kidney disease as a result of renal accumulation of autoimmune IgA complexes.

Divergent roles of ALS-linked protein FUS/TLS and TDP-43 intersect in processing long pre-mRNAs

Lagier-Tourenne, C. *et al. Nat. Neurosci.* doi:10.1038/nn.3230 (30 September).

The authors identified common mRNA targets regulated by two amyotrophic lateral sclerosis (ALS)-associated proteins, FUS/TLS and TDP-43. These common targets were transcribed from genes with very long introns that encode proteins important in neuronal integrity. The amounts of several of these proteins were reduced in ALS neurons, and the authors suggest that dysregulation of FUS/TLS or TDP-43 can elicit a common pathogenic pathway in ALS.