DEPRESSION

Ketamine steps out of the darkness

The way in which ketamine exerts its antidepressant effects has been perplexing. Evidence that a metabolite of the drug is responsible, and acts on a different target from ketamine, might be the key to an answer. SEE ARTICLE P.481

ROBERTO MALINOW

The novelist William Styron, who experienced depression, referred to the disorder as a black and howling tempest in the brain, noting[1] that "the wisest books among them underscore the hard truth that serious depressions do not disappear overnight". Indeed, depression is a painful and often deadly disorder that frequently requires months or more of treatment and that, for around one-third of sufferers, is treatment-resistant[2]. Ketamine is an attractive therapeutic, because it can act rapidly and effectively against even treatment-resistant depression[3–6] — but the drug has side effects and does not always work. An understanding of ketamine's mechanism of action, which could lead to improved treatments, has been widely sought. In this issue, Zanos *et al.*[7] (page 481) provide several lines of evidence to indicate that it is not ketamine itself, but one of its metabolites, that is responsible for the drug's antidepressant effects.

Ketamine has a moderately high binding affinity for, and can block the activity of, the NMDA receptor protein (NMDAR)[8]. This receptor is perhaps best known for its requirement[9] in a phenomenon called long-term potentiation (LTP), which occurs widely in the brain, whereby the synaptic connections between neurons are strengthened, enhancing neural signalling[10]. The enhanced signalling produced by LTP underlies the formation of associative memories[11,12].

How can transient blockade of NMDAR, and possibly LTP, have a rapid and long-lasting effect on human depression? Given the role of LTP in memory formation, it might be logical to assume that ketamine causes a brief block in the formation of memories. But even if this were true, how could it alleviate depression? To many physiologists, the idea that blocking NMDAR could treat depression has made no sense.

Zanos and colleagues' initial experiments placed doubt on an NMDAR-mediated mechanism of action by ketamine (Fig. 1). The authors compared the effects of two different structural forms, or enantiomers, of ketamine, called (*S*)- and (*R*)-ketamine, which are normally administered together. (*S*)-Ketamine is three to four times better at blocking NMDAR than (*R*)-ketamine[13], and so is predicted to be the better antidepressant under the NMDAR-inhibition model. However, the authors found that (*R*)-ketamine was several times more efficient at reducing depression-like behaviours in mouse models of depression. Furthermore, they confirmed[14] that an even more potent NMDAR inhibitor, which binds to the same site as ketamine, fails to produce sustained antidepressant-like effects.

So what could be responsible for the effects of ketamine treatment? The first hint came from comparing the drug's activity in male and female mice. Zanos *et al.* confirmed a previous observation[15] that a lower dose of ketamine is needed to reduce depression-like behaviours in females than in males. This could not be explained by different levels of ketamine in the brain. However, the authors found that levels of the ketamine metabolite hydroxynorketamine (HNK) were several-fold higher in the brains of females than males after the animals were given the same dose of the drug. Reducing the metabolism of ketamine to HNK reduced the effectiveness of ketamine towards depression-related behaviours in mice. Moreover, treating animals with HNK produced the same rapid and sustained antidepressant-like effects seen after treatment with ketamine. As with ketamine, the (*R*)-enantiomer of HNK had more-potent antidepressant-like effects than the (*S*)- form. And, importantly, the researchers showed that HNK neither binds to nor inhibits NMDAR.

The finding that the antidepressant effects of ketamine are not mediated through its actions on the NMDAR is a major advance. Nevertheless, it leads to an obvious, unanswered question — what is the molecular target of HNK responsible for these effects? This question should engender much activity by academic scientists, and possibly by large pharmaceutical companies that have been pouring capital into developing NMDAR inhibitors for treating depression. Candidate targets will probably soon emerge.

Although Zanos and colleagues did not identify such a target, they examined the role of another neural receptor protein, AMPAR, which is concentrated at synapses and mediates most neurotransmission in the brain. They found that a drug called NBQX, which reduces AMPAR activity throughout the brain,

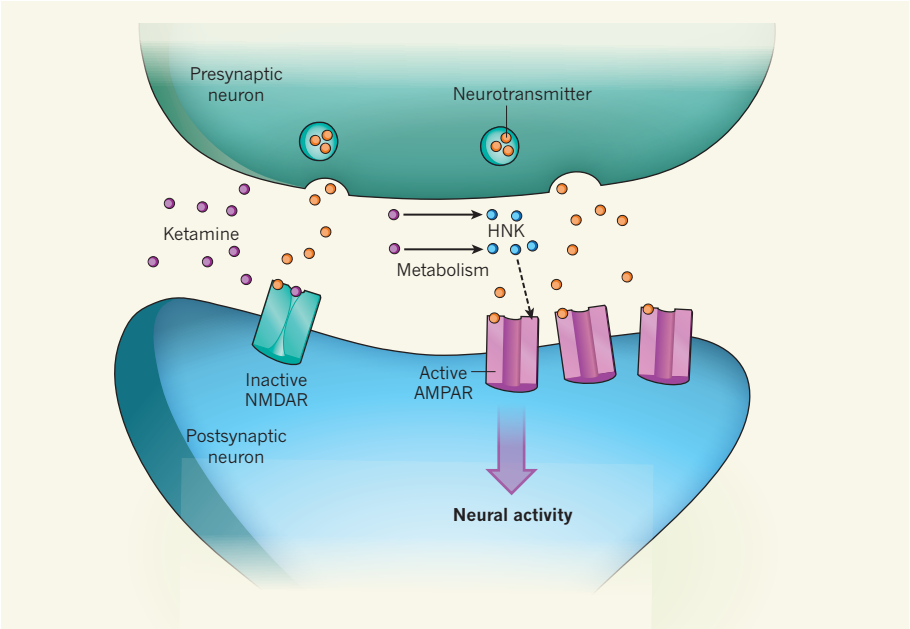

Figure 1 | Metabolite mediator of ketamine. How the drug ketamine exerts its antidepressant effects is unknown, although a common hypothesis states that it acts by binding to the receptor protein NMDAR on postsynaptic neurons, preventing neurotransmitter molecules released by presynaptic neurons from activating NMDAR and so inhibiting signalling processes triggered by the receptor. By contrast, Zanos *et al.*[7] report that it is a metabolite of ketamine called hydroxynorketamine (HNK) that has antidepressant activity. They provide evidence that HNK, through unknown intermediates, increases the levels of another neuronal receptor protein, AMPAR, at synapses (dashed arrow), enhancing neural activity. But how this produces an antidepressant effect remains unclear.

prevented and even reversed the antidepressant-like effects of ketamine and HNK in mice. It is surprising that a drug that indiscriminately reduces transmission in almost every brain circuit could alter the very specific effects of HNK and ketamine. The authors also show that transient application of HNK produces a long-lasting increase in AMPAR-mediated synaptic transmission (Fig. 1). How this can alleviate depression is not clear, unless HNK acts specifically to modulate the synapses that exhibit reduced function during depression[16]. Such a targeted action for HNK remains to be demonstrated.

Finally, Zanos *et al.* show that HNK does not elicit several of the cognitive and motor side effects that have been linked to ketamine. As such, this study represents important progress. Nonetheless, the molecular target and mechanism of action of HNK remain to be defined. Such advances might further the development of more-specific and effective treatments, allowing people with depression to step out of the darkness of this disorder. ■

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ATMOSPHERIC SCIENCE

Unexpected player in particle formation

Three studies find that a family of organic compounds affects the formation and initial growth of atmospheric aerosol particles in clean air — with implications for our knowledge of the climate effects of aerosols. SEE LETTERS P.521 & 527

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Cloud droplets form when water condenses on microscopic aerosol particles[1]. A key source of new particles in the atmosphere is nucleation — the formation and growth of molecular clusters, which must then grow about 50 times larger if they are to act as efficient cloud seeds. Sulfuric acid has long been recognized as the key player in particle formation[2]. But two studies in this issue[3,4], and another published in *Science*[5], suggest that molecules called highly oxidized multifunctional organic compounds (HOM compounds) have an under-appreciated role in driving both particle formation and the initial growth of particles, especially in environments largely unaffected by anthropogenic pollution.

Understanding the differences between past and present particle formation and growth rates is crucial in quantifying the aerosol cooling effect[6], which has offset warming driven by greenhouse gases over the past century, but remains highly uncertain[7]. Atmospheric sulfur emissions are higher today than in pre-industrial times because of increased fossil-fuel combustion[8], so to understand how particles affected the climate in the past, and how they affect pristine regions of the atmosphere today, it is necessary to characterize particle formation and growth when sulfuric acid concentrations are low. The latest studies together indicate that HOM compounds are key players.

HOM compounds form when hydrocarbons and other volatile organic compounds (VOCs), emitted into the atmosphere from many natural and anthropogenic sources, react with atmospheric oxidants, such as ozone[9,10]. They are diverse, containing varying numbers of molecules from a wide range of chemical groups, including alcohols and peroxides. Consequently, their vapour pressures — a property that determines their ability to condense — vary by more than 15 orders of magnitude[4].

Kirkby *et al.*[3] (page 521) investigated how effective HOM compounds are at producing new particles with diameters larger than 1.7 nanometres at low sulfuric acid concentrations, whereas Tröstl *et al.*[4] (page 527) determined the role of HOM compounds in the particles' subsequent growth (for particles starting at about 2 nm in diameter and increasing to about 20 nm). Both studies were performed in the laboratory, and used a VOC called α-pinene — a molecule emitted by trees and from the ocean — as the source of HOM compounds.

In their study, Kirkby *et al.* demonstrate that HOM compounds can nucleate to form particles without sulfuric acid, and that the particle-formation rate depends on the presence of Galactic cosmic rays (GCRs). Although previous observations[11,12] showed that organic compounds can enhance sulfuric acid-driven particle-formation rates, a direct demonstration of particle formation by organics in the absence of sulfuric acid had been elusive. The dependence of the organic-driven particle-formation rate on GCRs provides a potential connection between the magnetic variability of the Sun (which affects the GCR flux to Earth), particles and climate, an association that remains widely debated.

Newly formed nanoparticles grow through condensation. The growth stage is crucial for particles less than 10 nm in diameter, because they are especially prone to being absorbed by larger particles on collision, thus removing potential cloud seeds from the atmosphere. Nanoparticle-growth rates increase with diameter[13], perhaps because of condensation of organic compounds[14], but disentangling the controlling factors has been challenging.

Tröstl *et al.* show that the Kelvin effect — in which the volatility of liquids increases when their interface with the surrounding vapour is curved — rapidly decreases at nanoparticle surfaces as the particles grow. This allows increasingly efficient condensation of HOM compounds that have progressively higher (but always very low) volatilities as the particles grow. Importantly, the accelerating growth rates directly result from the fact that HOM compounds have a distribution of volatilities.

In complement to the two laboratory studies, Bianchi *et al.*[5] used field observations made at the Jungfraujoch research station in Switzerland (Fig. 1) to show that, when sulfuric acid concentrations are low, particle formation and accelerating growth are indeed efficient only when concentrations of HOM compounds are sufficiently large. Although the observed particle-formation rates are in reasonable agreement with Kirkby and colleagues' results, Bianchi *et al.* were unable