CIRCADIAN RHYTHMS

Depression brought to light

Exposure to abnormal light–dark cycles causes depression-like behaviour and learning deficits in mice. The defects seem to occur independently of disturbances to sleep and other processes regulated by the biological clock. SEE LETTER P.594

LISA M. MONTEGGIA & EGE T. KAVALALI

Changes in environmental light can alter mood and adversely affect cognitive function[1]. Nonetheless, the identity of the neuronal circuitry involved in light-mediated regulation of mood and cognition, and how it functions, are poorly understood. A prevailing hypothesis is that, because alterations in light disrupt circadian rhythms (processes that are controlled by our in-built 24-hour 'biological clock'), including sleep, they then indirectly alter mood and impair learning. On page 594 of this issue, LeGates *et al.*[2] explore the link between the effects of light on the circadian system and dysfunctional mood regulation, and begin to delineate the underlying neural circuitry. They provide convincing evidence that abnormal light exposure can directly affect mood and learning*.

LeGates and colleagues exposed mice to 3.5 hours of light followed by 3.5 hours of dark (T7 light cycle), instead of the normal 12-hour light and 12-hour dark cycle. They then examined the effects of this abnormal light cycle on depression-like behaviour, and on learning and memory. The T7 cycle did not alter the total amount of sleep the mice had, suggesting that any physiological effects were independent of sleep deprivation. Moreover, it did not cause significant disruption to circadian rhythms; that is, the biological clocks, which regulate physiological activities in relation to circadian environmental cycles, remained intact and in phase with one another.

Nevertheless, mice experiencing the T7 cycle showed increased depression-related behaviour, along with increased levels of the hormone corticosterone, a potential link to depression. The mice were also impaired in some forms of learning and memory, as indicated by alterations in the extent of long-term potentiation (LTP) — an increase in the strength of synaptic connections between neurons that correlates with learning and memory — in the brain's hippocampus region. However, long-term synaptic depression (a decrease in strength) was unaffected, suggesting that light-induced changes are specific to synaptic strengthening.

*This article and the paper under discussion[2] were published online on 14 November 2012.

Physiological functions such as sleep and metabolism are tightly regulated by circadian rhythms that are entrained by ambient light exposure[3]. Light is classically detected by photon-sensitive neurons — rods and cones in the retina of the eye — which relay information to retinal ganglion cells (RGCs) that, in turn, project to higher brain regions for image formation. However, a population of intrinsically photosensitive RGCs (ipRGCs), which express the photopigment melanopsin and are distinct both from other RGCs and from rods and cones, mediate non-image-forming processes in response to light[4,5]. The light sensitivity of melanopsin matches that of non-image-forming, but light-dependent, physiological processes that are regulated in a circadian manner, including locomotion and the pupillary light reflex[6,7].

"This investigation provides a detailed road map by which to pursue understanding of the impact of light on mood and cognitive function."

To examine whether the traits seen with the T7 light cycle were due to direct effects of light — independent of image-forming processes — LeGates and colleagues exposed mice that lacked ipRGCs to this light cycle. The ipRGC-deficient animals did not show alterations in depression-like behaviour, learning or LTP. The authors therefore conclude that light acting on ipRGCs directly contributes to mood regulation and learning.

These findings support the use of the T7-light-cycle paradigm as an animal model of depression, and particularly for evaluating antidepressant treatments. Existing paradigms tend to rely on the behavioural-despair model, which assesses how quickly an animal 'gives up' in an inhospitable situation and evaluates antidepressants by whether they can improve performance. Diversification of behavioural paradigms may help to uncover clinically applicable drug targets that could not be identified by these traditional approaches, and which may lead to more reliable and faster-acting antidepressants.

The study raises intriguing questions regarding the mechanisms and specific neuronal targets of ipRGCs in mediating the effects of light on the regulation of mood and cognitive function. For instance, it suggests that not only activation of ipRGCs but also changes in the long-term pattern of ipRGC exposure to light lead to synaptic plasticity (modification of the strength of neuronal synapses, which may underlie changes in behaviour). It remains unclear whether this effect is caused by changes in the synaptic strengths of ipRGCs themselves or by regulation of their downstream neuronal targets. LTP deficits seen in hippocampal synapses point to more general changes in plasticity, beyond the immediate synaptic projections of ipRGCs. The direct targets of ipRGC projections[8] (including, but not limited to, the suprachiasmatic nucleus, the intergeniculate leaflet and the olivary pretectal nucleus) that mediate these synaptic abnormalities should be identified.

Interestingly, LeGates *et al.* report that long-term treatment with the antidepressant drugs fluoxetine and desipramine reverses some of the behavioural effects of the T7 cycle, as well as the associated LTP deficit. This indicates that the same neuronal-circuit elements, and possibly neurotrophic factors (which mediate neuronal growth), that, according to traditional models, mediate depressive-like behaviour, are involved in the depressive response to abnormal light exposure.

However, sensitivity to long-term antidepressant administration is a hallmark of behavioural paradigms that depend on chronic stress induction, such as social defeat[9] (in which an animal repeatedly loses confrontations with another animal of the same species). Consequently, it should be further explored whether some of the more general synaptic plasticity reported by LeGates *et al.* is associated with stress due to exposure to the T7 cycle. It would also be of interest to test whether depressive-like behaviours respond to faster-acting antidepressants such as ketamine, which alleviate symptoms within hours[10]. Response to ketamine administration would help to determine whether these light-induced abnormal behaviours are as reversible in the short term as are depressive-like traits elicited during behavioural despair.

LeGates and co-workers' thorough investigation provides a detailed road map by which to pursue understanding of the impact of light on mood and cognitive function. Dissecting the direct effect of ipRGC synaptic projections on mood and cognition will not only elucidate a rather enigmatic neuromodulatory pathway, but may also provide new neuronal targets for treatments for mood and cognitive disorders. ■

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MICROBIOLOGY

A piece of the methane puzzle

The identification of a sea-floor microorganism that single-handedly conducts anaerobic oxidation of methane changes our picture of how the flux of this greenhouse gas from the ocean to the atmosphere is regulated. SEE ARTICLE P.541

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Methane is a potent greenhouse gas[1] that exists in immense amounts in sea-floor sediments across the globe[2]. The flux of this methane to the atmosphere can profoundly affect global climate, and previous episodes of rapid climate warming have been ascribed to oceanic methane emissions[3]. Marine microorganisms that perform anaerobic oxidation of methane (AOM) act as gatekeepers of these sea-floor reservoirs, moderating gas flux from the ocean to the atmosphere. However, despite a strong research effort aimed at understanding its regulation, the process of AOM has mystified biogeochemists and microbiologists for decades. On page 541 of this issue, Milucka *et al.*[4] describe a single microorganism that can mediate both the oxidative and reductive processes of AOM — a finding that transforms our understanding of both methane and sulphur cycling in the present, past and future environments of Earth*.

Sulphate-linked AOM was first proposed as an explanation for the profiles of dissolved sulphate and methane that are trapped within pore spaces in coastal marine sediments[5]. Twenty years later, AOM was suggested to be a cooperative metabolic process[6], mediated in marine environments by associations between anaerobic methanotrophic archaea[7,8] (ANMEs) and sulphate-reducing bacteria. (The archaea are a domain of single-celled, but not bacterial, microorganisms.) Together, these microorganisms were thought to oxidize methane to carbon dioxide while reducing sulphate (SO_4^{2-}) to hydrogen sulphide (H_2S), splitting the energy supplied by this coupled process between them (Fig. 1a). More recently, two alternative mechanisms of AOM were discovered: one involving the coupling of methane oxidation to the reduction of reactive metals, also presumed to be mediated by cooperating microorganisms[9] (Fig. 1b) and the other mediated by an extremely unusual bacterium, *Methoxymirabilis oxyfera*, that makes its own oxygen to fuel AOM in anoxic environments without the aid of a metabolic partner[10] (Fig. 1c).

Now, Milucka *et al.* reveal a fourth mechanism for AOM. The authors report that archaea of the ANME-2 clade use an unusual sulphate-reduction strategy to single-handedly mediate both AOM and sulphate reduction, thereby keeping the energy derived from both reactions mostly to themselves and eliminating the need for a microbial partner for the shuttling of electrons or metabolites. Their work hinged on a culture of microorganisms originally obtained from sea-floor sediments from a Mediterranean mud volcano, Isis, which was enriched in microorganisms involved in AOM over eight years of culture[11]. The previous lack of such microbial isolates has been a major stumbling block in efforts to unravel the mechanisms of AOM.

With this culture in hand, Milucka *et al.* used a dazzling array of geochemical, molecular biological and microbiological techniques, combined with some clever physiological sleuthing using bacterium-specific antibiotics to link the observed sulphate-reduction activity to the archaea, to show that

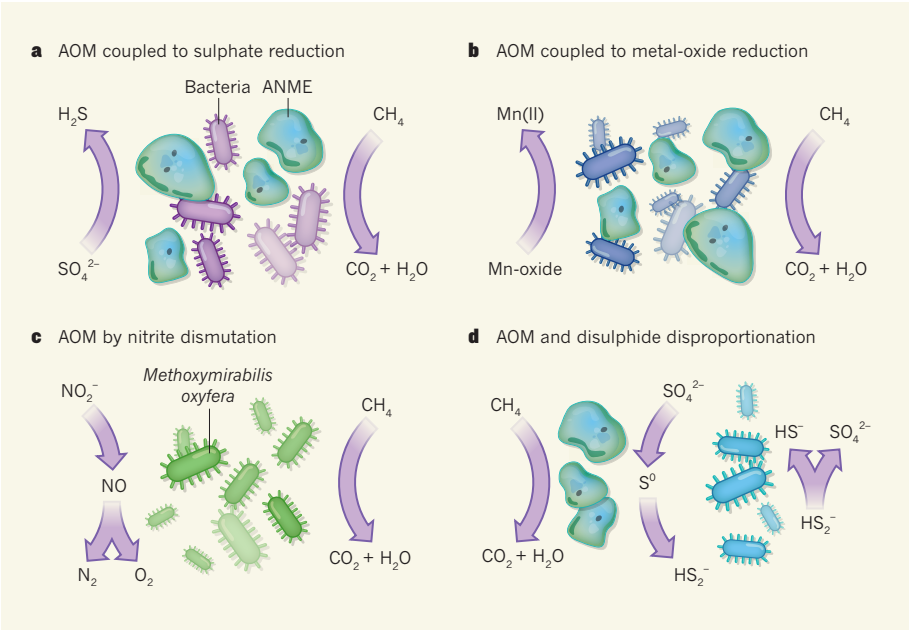

Figure 1 | Modes of microbial anaerobic methane oxidation. There are four known ways in which microorganisms achieve anaerobic oxidation of methane (AOM). Two of these (**a**, **b**) are thought to rely on obligate associations between two or more microbial partners, one of which performs oxidation and the other reduction; in the other two cases (**c**, **d**), a single microorganism performs both reactions. **a**, Anaerobic methanotrophic archaea (ANMEs) oxidize methane (CH_4) and convert it to carbon dioxide and water, in cooperation with sulphate-reducing bacteria, which convert sulphate (SO_4^{2-}) to hydrogen sulphide (H_2S) (ref. 8). The mechanism of energy exchange between the ANMEs and the sulphate-reducing bacteria is unknown. **b**, The oxidation of methane to CO_2 by ANMEs is coupled to the reduction of metal oxides, whereby metals such as manganese (Mn) or iron (Fe) are reduced to the +2 oxidation state[9]. **c**, The bacterium *Methoxymirabilis oxyfera* converts nitrite (NO_2^-) to nitric oxide (NO) and then dismutates (splits) NO into nitrogen and oxygen as diatomic gases. The bacterium then uses the resulting O_2 to support methane oxidation[10]. **d**, Milucka *et al.*[4] show that some ANMEs oxidize methane (as in **a**) but also reduce sulphate to zero-valent sulphur (S^0), which they produce in the form of disulphide (HS_2^-). The disulphide can be used by associated bacteria, Deltaproteobacteria, to yield sulphide (HS^-) and sulphate, but this is an association of convenience, rather than necessity.

*This article and the paper under discussion[4] were published online on 7 November 2012.