suggesting that tropical deforestation may have contributed to the decrease.

Methane absorbs solar radiation strongly at infrared wavelengths, and is second only to carbon dioxide in its role in producing an enhanced greenhouse effect and warming the Earth. It also affects the way the atmosphere cleans itself of pollutants, and influences ozone depletion through the production of water vapour in the stratosphere. So methane has been the subject of intense scientific and political scrutiny, and is targeted for emissions controls under the Kyoto Protocol on climate change.

The predominant sources of atmospheric methane are biological. The main ones previously recognized were microbial activity in wetlands (including natural swamps and rice paddy fields) and the eructations of ruminant animals. The dramatic upswing in agriculture required to feed the Earth's growing population has led to huge increases in rice culture and livestock farming in the past 250 years. The result has been large rises in methane emissions from both of these sources.

It was thought that methane production in flooded paddy fields was due to microbial activity in the anoxic environment of the paddy soils. In a 'Kyoto world', in which sources and sinks of greenhouse gases are added and subtracted like the columns in an accountant's report, there are claims that new, 'drier' forms of paddy-field irrigation will lead to reduced methane emissions. But a study of rice plants has shown a strong link between the number and size of leaves on the plant and methane emissions[6]: could the rice plants themselves be as significant a source of methane as the flooded paddy fields?

The implications of Keppler and colleagues' work for the Kyoto Protocol include how reforestation and ruminant animals are treated in methane budgets. Under the Kyoto rules, reforestation since 1990 may be used as a CO_2 sink to offset greenhouse-gas emissions from other sources; we now have the spectre that new forests might increase greenhouse warming through methane emissions rather than decrease it by sequestering CO_2. And in certain countries with large numbers of sheep, cattle and other ruminant livestock, methane constitutes a significant fraction of total greenhouse-gas emissions. In such countries — Ireland and New Zealand, for example — ruminant animals graze on pastures that were originally forested. Given the findings of Keppler *et al.*, it is possible that the forests that once occupied pasture may have produced as much methane as ruminants and grasses on the same land.

The new work will also influence studies of the history of Earth's climate. Indications of past climate are often deduced from analyses of the concentration and isotopic composition of greenhouse gases in tiny air bubbles trapped in polar ice cores. Keppler and colleagues' study shows that, in pre-industrial times, the relative contribution of methane to the atmosphere by direct emissions from plants could have been much larger than it is today. Measurements of isotopic values in methane derived from Antarctic ice cores show a signal between AD 0 and 1200 that is inconsistent with theories of methane budgets being dominated by wetland sources[7]. A pre-industrial atmosphere containing large contributions of methane derived from vegetation can account for the observed isotopic signal. One of the further avenues of research will centre on the role of methane and vegetation in glacial–interglacial transitions.

This paper[1] will undoubtedly unleash controversy, not the least of which will be political. But there are many scientific questions to be addressed. How could such a potentially large methane source have been overlooked? And what kind of mechanism could produce a highly reduced gas such as methane in an oxic environment? There will be a lively scramble among researchers for the answers to these and other questions. ■

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BEHAVIOUR

Smells, brains and hormones

Gordon M. Shepherd

Contrary to the traditional view, the main olfactory pathway can mediate responses to pheromones as well as to common odours. Recent studies show that pheromone-activated hormonal systems extend widely within the brain.

Pheromones are powerful species-specific chemical signals that organize a wide range of the social conduct of animals, such as mating behaviour, social dominance, aggression, and bonding of a mother with her young. A common belief is that in mammals pheromones are detected only by a specialized sensor in the nose known as the vomeronasal organ, and that the main olfactory epithelium, which lines the nasal cavity, is responsible only for sensing common odours (Fig. 1, overleaf). A long line of under-appreciated work has suggested that this view is too restrictive. Three papers[1–3] apply the *coup de grâce*, indicating that we need to rethink entirely how pheromones control hormonal responses, not only in mammals generally, but in humans in particular.

In mammals, female mating and reproductive behaviour are controlled by a group of neurons in the hypothalamus, the brain's chief hormonal, or endocrine, control centre. These particular neurons secrete 'luteinizing hormone-releasing hormone' (LHRH; also known as gonadotrophin-releasing hormone, or GnRH) into the hypothalamic–pituitary system to control gonadal and steroidal functions[4,5]. As they report in *Cell*, Yoon *et al.*[1] and Boehm *et al.*[2] have developed ingenious methods to trace the brain systems that connect to these neurons.

Yoon *et al.*[1] used a fluorescent virus that is transported only backwards across the junctions (synapses) between neurons; that is, it will follow the path of a neuronal input to its point of origin. They genetically engineered mice to express a factor specifically in the LHRH neurons that would allow the uptake of the virus into only these cells. So, when the virus is injected into the hypothalamus of the mice, its progress can be traced backwards from the LHRH cells over at least two synapses along the circuits related to these neurons.

The cells that first take up the virus are in the expected hypothalamic areas. However, tracing backwards, labelling occurred in many brain regions, indicating a complex system of mainly olfactory regions and somatosensory areas (dealing with sensations in the body). In the olfactory brain regions, fluorescence was found in the olfactory cortex, the main olfactory bulb, and even out into the main olfactory epithelium. Contrary to predictions from the traditional view, none was seen in the 'accessory' pheromone pathway that originates in the vomeronasal organ. Moreover, behavioural experiments showed that chemosensory modulation of activity in LHRH neurons is primarily through the main olfactory pathway. The results extend previous indications (summarized in ref. 3) that the main olfactory pathway triggers generalized mating behaviour, whereas the vomeronasal pathway mediates specific male and female cues.

Boehm *et al.*[2] took a different approach. They

engineered mice to contain a gene encoding barley lectin (BL), a tracer molecule that is transferred in both directions across synapses. The BL gene was placed next to the regulatory region for the gene encoding LHRH, so that BL was produced in LHRH cells. In the hypothalamus, expression of BL was limited to some 800 LHRH neurons. From there, it was transferred to the 'vomeronasal amygdala', where the accessory pathway ends, implying that the LHRH neurons are connected to neurons associated with vomeronasal input, either receiving signals from and/or feeding back to the accessory pathway. These same neurons were activated by exposure of the animal to pheromones, showing that these neurons are indeed in the vomeronasal pathway to the LHRH system in the hypothalamus.

There were also some BL-positive neurons in the olfactory cortex and amygdala in the main olfactory pathway, and some of these responded to pheromones. Patterns of neuronal activity markers suggested that pheromone signals can be relayed through the olfactory cortex to LHRH neurons, and that LHRH neurons can in turn feed back through the cortex to the accessory pathway to modulate incoming signals. Many additional brain regions contained BL$^+$ neurons, and some of these also contained LHRH$^+$ fibres. These findings are consistent with previous work[4,5] showing that the hypothalamic core has an extraordinarily far-reaching system of neural inputs and outputs.

The question of whether the main olfactory or accessory pathway controls this system has been addressed by Mandiyan *et al.*[3]. The sensory cells in the main pathway use a membrane channel known as Cnga2 to turn the receptor response into the electrical impulse code. So the authors examined male mating behaviour in mutant mice that lack Cnga2. They found that the mice showed deficiencies in each of the steps involved in mating — sniffing, mounting and intromission — compared with normal controls. Because Cnga2 is not expressed in vomeronasal sensory cells, this indicates that the main olfactory pathway has a "broad and essential" role in mating[3].

These results are of interest for several reasons. Hormone-secreting cells in the mammalian brain were first identified in the hypothalamus in the 1950s (reviewed in ref. 6). The recent[4] and current[1–3] studies show that, in addition to the main and accessory olfactory pathways, this neuroendocrine system includes circuits involved in sexual behaviour, reproduction, arousal, reward, appetite, defensive behaviour and movement. This system for coordinating the neuroendocrine state of the animal with its mating and reproductive activities seems to operate in parallel with the central neurotransmitter systems for noradrenaline, acetylcholine and serotonin that function as a self-governing internal autonomic system for modulating behavioural states throughout the brain. It also interacts intimately with the immune system (see below).

The evidence that the neuroendocrine system can be controlled by both common odours and pheromones acting through the main olfactory pathway confirms and extends previous studies. For example, the suckling pheromone in rats activates a special part of the main olfactory bulb[7]. The male hormone androstenone stimulates mating behaviour in boars despite removal of the vomeronasal pathway[8]. Urinary pheromones elicit activity patterns in the main olfactory glomerular layer[9,10]. Mitral cells in the main olfactory pathway respond to urinary social signals[11]. Pheromones stimulate olfactory as well as vomeronasal sensory neurons[12]. And amazingly, a new class of pheromones — non-volatile MHC class I peptides — activate both olfactory and vomeronasal sensory neurons, with the vomeronasal pathway being required for the Bruce effect (pregnancy termination)[13] and the main pathway being required for mating preference[14].

Together, these findings revolutionize our understanding of the role of smell in controlling the neuroendocrine brain. The traditional distinction that common odours are perceived through the olfactory pathway and pheromones by the vomeronasal pathway is dead. Each pathway must be assessed for a putative pheromone on its own evidence. Humans lack a functional vomeronasal system, but brain scans show that sex pheromones activate wide regions of the human brain, including the cognitive areas[15], implying that, as in the rodent, the pheromone-activated endocrine system is much more extensive than previously realized. We have much more to learn about how intimately neuroendocrine functions, controlled by pheromones acting through our noses, interact with other operations within the brain to control human behaviour and cognition. ■

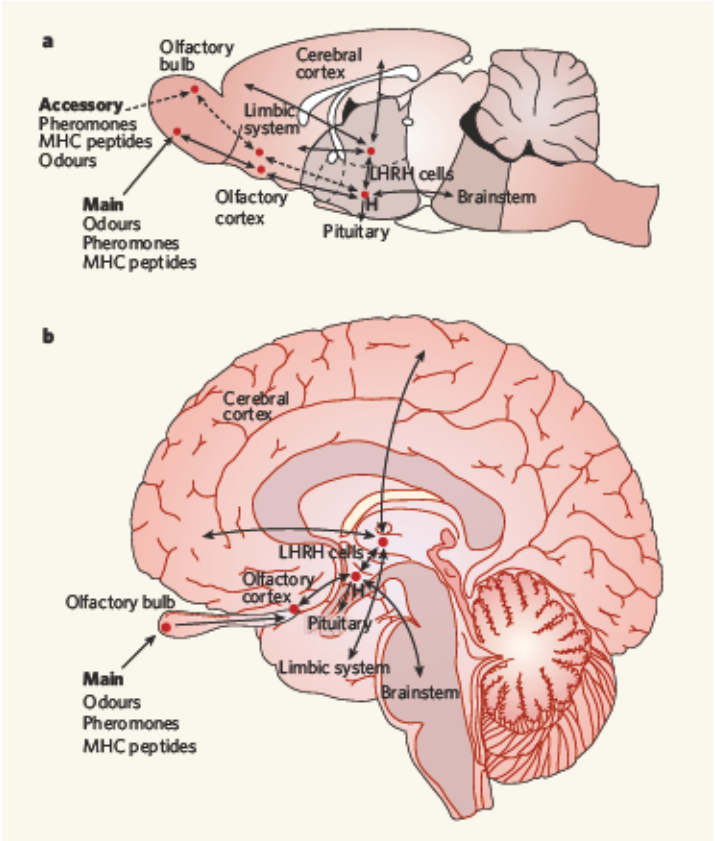

Figure 1 | Brain circuits for pheromones. **a**, A side view of the rodent brain, showing the main (solid lines) and accessory (dashed lines) olfactory systems feeding into the hypothalamus (bold H) and related regions, with connections from the hypothalamus to the cerebrum (for perception and emotion), limbic system and brainstem (for olfactory-guided mating and reproductive behaviour) and pituitary (for coordination of endocrine functions). The new studies[1–3] highlight the extensive connections of cells expressing luteinizing-hormone releasing hormone (LHRH), showing that the main olfactory pathway is key in mediating pheromonal inputs to them. **b**, Implications for the human brain. In the human brain, only the main olfactory pathway is functional, presumably mediating pheromonal and other olfactory inputs to most of the central LHRH brain systems corresponding to those in the rodent, as well as to cognitive and other regions shown by functional imaging[15].

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