New pathways in the treatment for menopausal hot flushes

Within the next 25 years, an estimated 1 billion women worldwide will be older than 50 years, and therefore likely to be nearing menopause or postmenopausal.1 Hot flushes (vasomotor symptoms) are experienced by approximately 73% of postmenopausal women, and the associated sleep disturbances, fatigue, and decreased cognitive function lead to a reduction in their quality of life and an increased use of medical resources.2 A hypothalamic mechanism is well established in the understanding of hot flushes,3 but the pathways involved have been unclear, thus reducing therapeutic options. Novel hypothalamic neuropeptide-signalling pathways have shed light on the central regulation of both reproductive and thermoregulatory systems and the links between them,4 and might now lead to specific therapies.

The menopause results in oestrogen deficiency, with loss of feedback regulation of hypothalamic gonadotropin-releasing hormone (GnRH). The kisspeptin-neurokinin B (NKb)-dynorphin (KNDy) signalling system in the hypothalamus is the proximate and obligate stimulus of GnRH secretion, and is hypertrophied after the menopause.43 Hypothalamic NKb neurons also project to the medial preoptic area, the hypothalamic site of thermoregulatory neuronal pathways, and evidence exists that these NKb neurons are a key link between the endocrine changes of the menopause and vasomotor symptoms.4 Flushing, like thermoregulation, is controlled centrally but effected peripherally, and blood flow to the skin is also increased in postmenopausal women with severe flushing.4 NKB neurons might also facilitate cutaneous vasodilatation and contribute to oestrogenic modulation of body temperature.5

In The Lancet, Julia Prague and colleagues4 report the findings from their phase 2, randomised, double-blind, placebo-controlled trial investigating the oral neurokinin 3 receptor (NK3R) antagonist MLE4901 as a new therapy for menopausal hot flushes. In 28 healthy women aged 40–62 years, oral administration of a
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40 mg dose twice per day for 4 weeks reduced the number of hot flushes during week 4 by 45 percentage points (95% CI 22–67) compared with placebo (intention-to-treat adjusted means: placebo 49.01 [95% CI 40.81–58.56] vs MLE4901 19.35 [15.99–23.42]; adjusted estimate of difference 29.66 [17.39–41.87]; p<0.0001). This finding was also supported by an objective assessment of flushes, using the Bahr sternal skin conductance monitor. Reductions in the number of flushes might be less important to women than measures of quality of life, thus it is of interest that the authors found hot flush severity, bother, and interference to be significantly reduced during treatment with MLE4901. However, in Prague and colleagues’ study, no improvements occurred in the sexual symptoms commonly reported after menopause (MENQOL sexual domain score adjusted means: placebo 2.15 [95% CI 1.84–2.51] vs MLE4901 1.98 [1.68–2.30]; p=0.24). As an index of GnRH secretion, luteinising hormone pulse frequency was unchanged in the treatment group, although other measures of pulsatile secretion altered with increases in amplitude and orderliness of luteinising hormone pulse. Thus, although NKB pathways regulate both the vasomotor and reproductive systems, separate effects can be identified, and these might vary with the endocrine environment. Most withdrawals from the study were for reasons unrelated to treatment, and no serious adverse events occurred with MLE4901, although three women developed liver enzyme elevations (alanine aminotransferase was 4.5–5.9 times the upper limit of normal), which normalised within 90 days. The limitations of the trial include its small size (of 68 women screened, only 28 completed the trial and were included in the per-protocol analysis) and short duration of treatment.

The current gold-standard treatment for menopausal hot flushes is oestrogen, but in some women its maximum efficacy might take many weeks to achieve. Selective serotonin-reuptake inhibitors are a non-hormonal alternative with similar improvements in flush reduction, but might not be well tolerated. And, although oestrogen is an effective treatment for flushing, oestrogen-free therapies are necessary for women with breast cancer. The severity of hot flushes in these women might be a major contributor to reduced adherence to the recommended 10 years of endocrine therapy, increasing recurrence and mortality. Additionally, hot flushes are not the sole preserve of women: 44–80% of men treated for advanced prostate cancer have hot flushes, and 25% describe them as the most significant adverse effect on their quality of life.

Although the role of oestrogen in the maintenance of bone and cardiovascular health is crucial to post-reproductive health and quality of life during older age, vasomotor symptoms are the most commonly reported, and often the most acutely distressing, symptom of menopause. Therefore, NKB antagonists are an exciting development in an area in which the last development in mechanistic understanding is more than 20 years old. Larger trials of clinically relevant duration examining benefits relative to established treatments are needed and might lead to a much needed addition to a very small toolbox of treatments for hot flushes.

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JS declares no competing interests. RAA has received consultancy fees relating to MLE4901 (previously named AZD4901), the drug discussed in this Comment, for polycystic ovary syndrome and research support (supply of AZD4901) for a range of studies, including in postmenopausal women, from AstraZeneca; advisory board fees from Takeda Pharmaceuticals unrelated to research on MLE4901; and consultancy fees from NeRRe Pharmaceuticals on a related drug (NT814) across a range of indications, including menopause; and has a patent PCT/GB2015/050494 for AZD4901 for female contraception pending to the University of Edinburgh.

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Paralysis of the arms and hands due to disease or trauma of the CNS greatly impairs the quality of life of millions of individuals. Therapies that replace lost neurons or repair severed connections hold great promise, but are probably years away from clinical deployment. Neuroprosthetics offer an alternative approach to restoring function, without relying on repair of damaged tissue, that is based on two fundamental premises. The first premise is that when we move a body part, or even imagine moving, moment-to-moment information that describes the movement can be decoded from measurements of the electrical activity in certain regions of the brain. 1 Even in individuals who can no longer move due to CNS damage, desired movements are still represented in the activity of cortical neurons. 2 This information can be transformed with mathematical algorithms into signals that can control a device outside the body. This strategy has enabled human subjects in laboratory settings to control, in real time, computer cursors or robotic arms with brain activity. 3,4 The effectiveness of such brain–machine interfaces is dependent on the second premise: the brain can modify its activity on the basis of feedback about the success of the movement, to improve performance. 5 Over an individual’s lifetime, the brain learns patterns of activity that produce accurate, smooth movements of the person’s own body. But the brain is remarkably adaptable and can learn to generate new patterns appropriate for the control of an external device, with actuators and mechanical properties that behave differently to muscle, tendons, and joints.

An even more ambitious neuroprosthetic uses decoded brain activity to reanimate paralysed limbs. Electrical current applied to muscles, peripheral nerves, or the spinal cord can contract muscles in a controlled manner. 6 The goal is futuristic: a paralysed individual thinks about moving her arm as if her brain and muscles were not disconnected, and implanted technology seamlessly executes the desired movement. Both fundamental premises apply, but this type of neuroprosthetic requires the technology not only to record and decode neural signals, but to interface with the body’s motor system to produce complex patterns of muscle contractions. Results of only a few studies in animals 7,8 and one in human beings 9,10 have shown the feasibility of this approach.

In The Lancet, Abidemi Bolu Ajiboye and colleagues 11 have advanced the ability of a neuroprosthetic to reanimate a paralysed limb. They report the experience of a man with a functionally complete C4 spinal cord injury using a brain–machine interface to make purposeful reaching and grasping movements. He received implants of 192 microelectrodes in motor cortex to record the activity of many neurons, and 36 percutaneous electrodes for electrically stimulating hand and arm muscles. A novel algorithm mapped brain activity to stimulus parameters that produced specific joint movements. The participant learned to modulate cortical activity to move his arm to targets presented in a virtual-reality environment, and to reach, grasp, and drink from a cup of coffee and use a fork to eat mashed potatoes. After practising, he acquired and held virtual targets with 80–100% success, with reasonable speed, and without strong mental exertion. Without the brain–machine interface, he was unable to perform any useful movements.

This study is groundbreaking as the first report of a person executing functional, multijoint movements of a paralysed limb with a motor neuroprosthesis. However, this treatment is not nearly ready for use outside the lab. The movements were rough and slow...