Therapeutic stimulation of the hypothalamus: pathophysiological insights and prerequisites for management

Massimo Leone,1 Angelo Franzini,1 Giovanni Broggi,1 Arne May2 and Gennaro Bussone1

1Istituto Nazionale Neurologico Carlo Besta, Milan, Italy and 2Department of Neurology, Hamburg University, Hamburg, Germany

Correspondence to: Massimo Leone, MD, Istituto Nazionale Neurologico Carlo Besta, via Celoria 11, 20133 Milano, Italy. E-mail: leone@istituto-besta.it
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Sir,

We thank Dr Gupta for his interest in our work. Verapamil was in fact tried in this patient up to 960 mg day with no benefit (Attanasio et al., 2000), as were all known cluster headache (CH) prophylactics.

In our patient, the pain attacks were always accompanied by drug-resistant blood pressure crises (diastolic pressure up to 160 mmHg), during which repeated retinal and vitreous humour haemorrhages occurred, resulting in right eye blindness and severely compromised left visus—clear evidence of target organ damage. These hypertensive crises would inevitably have caused irreversible damage to other organs, had they not been controlled; they have not recurred since DBS.

Furthermore, the pressure crises only occurred with CH attacks, beginning at the same time but peaking long before the pain peak, indicating they were pain-independent. The patient also had sleep disturbances, hyperphagia, aggression and hypersexuality (Attanasio et al., 2000), all of which ceased completely under hypothalamic stimulation, thereby implicating the hypothalamus (Fig. 1).

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**Fig. 1** Scheme proposed to explain cluster headache crises and related phenomena in our patient.

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Increased calcitonin-gene related peptide (CGRP) levels in the ipsilateral jugular vein during CH crises have been described (Goadsby and Edvinsson, 1994) and attributed to trigeminal nerve activation. Thus, Gupta’s claim that in CH ‘CGRP reduction can contribute to hypertensive crises’ is incorrect.

Gupta’s assertion that verapamil and indomethacin do not freely cross the intact blood–brain barrier is also incorrect, as testified by abundant data (e.g. Bannwarth et al., 1990). Note too that indomethacin is not as important in CH treatment as Gupta claims: it is only a second-line therapy for acute attacks.

Gupta suggests next that hypothalamic stimulation probably does not work (in our patient) by activating pain-modulating pathways. However, direct connections between the hypothalamus and trigeminal nucleus caudalis are known in animals, explaining how the posterior hypothalamus affects painful inputs to the nucleus caudalis (Benjamin et al., 2004).

We find Gupta’s suggestion astonishing that a placebo effect of hypothalamic stimulation ‘is not easily excluded’ in our patient. He had undergone four ineffective demolitive procedures on the trigeminal; post-DBS follow-up is now more than 4 years and he remains attack-free. During that time the stimulator was turned off on several occasions (twice double-blind) and each time the headaches returned, to disappear when stimulation was resumed. These data exclude a placebo effect beyond reasonable doubt. However, Gupta raises a valid point about excluding a placebo effect for hypothalamic stimulation in general. There are various approaches: (i) cranial burr-hole but sham electrode implant; (ii) electrode implant at a different site; (iii) hypothalamic electrode implant but no stimulation; and (iv) hypothalamic electrode implant with stimulation at settings not usually effective.

The first two possibilities are ethically unacceptable; the third is problematic because most patients perceive correct stimulation. With regard to the fourth approach, experience on more patients with sufficiently long follow-up will unambiguously allow us to distinguish effective from non-effective parameters.

Gupta notes that alcohol, nitroglycerine and histamine can provoke CH attacks, but they do so only during the active illness phase, indicating that vasodilation per se is not sufficient to induce attacks, and that a permissive state—plausibly a central derangement—is a crucial prerequisite.

CH attacks may persist or recur after demolitive trigeminal surgery (Matharu and Goadsby, 2002), as occurred in our patient. This is good evidence for a mainly central origin of CH pain. Regarding Gupta’s suggestion that development of aberrant neural routes may be responsible for CH recurrence after surgical interruption of the trigeminal, we cite the CH patient of Matharu and Goadsby (2002), who had no CH remission after trigeminal sectioning. He did, however, have total trigeminal anaesthesia and absent blink reflex more than 10 years later, strongly suggesting no development of alternative nervous pathways.

We agree with Gupta that the pathogenesis of CH remains incompletely understood. We propose regarding it as a syndrome rather than simple illness, thereby emphasizing the contributions of both peripheral and central structures. That the peripheral nervous system plays a role in symptomatic CH is beyond discussion. That the hypothalamus is involved in most CH syndromes seems indisputable too: yet the two forms are often impossible to distinguish clinically. We suggest that primary CH is characterized by hypothalamic activation with secondary activation of the trigemino-facial reflex. In symptomatic CH, activation of the trigemino-facial reflex could occur directly or via the trigemino-hypothalamic pathway.

References