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REVIEW

Mechanisms of autonomic disturbance in the face during and between attacks of cluster headache

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Lacrimation and nasal secretion during attacks of cluster headache appear to be due to massive trigeminal-parasympathetic discharge. In addition, the presence of oculo-sympathetic deficit and loss of thermoregulatory sweating and flushing on the symptomatic side of the forehead indicate that the cervical sympathetic pathway to the face is injured in a subgroup of cluster headache patients. In this review, it is argued that a peripheral rather than a central lesion produces signs of cervical sympathetic deficit, probably resulting from compression of the sympathetic plexus around the internal carotid artery. Although trigeminal-parasympathetic discharge appears to be the main trigger for vasodilation during attacks, supersensitivity to neurotransmitters such as vasoactive intestinal polypeptide, together with release of sympathetic vasoconstrictor tone, may boost facial blood flow in patients with cervical sympathetic deficit. In addition, parasympathetic neural discharge may provoke aberrant facial sweating during attacks in patients with cervical sympathetic deficit. Although neither trigeminal-parasympathetic discharge nor cervical sympathetic deficit appears to be the primary trigger for attacks of cluster headache, these autonomic disturbances could contribute to the rapid escalation of pain once the attack begins. For example, a pericarotid inflammatory process that excites trigeminal nociceptors might initiate neurogenic inflammation and trigeminal-parasympathetic vasodilation. To complete the loop, neurogenic inflammation and trigeminal-parasympathetic vasodilation could provoke the release of mast cell products, which aggravate inflammation and intensify trigeminal discharge. □*Cluster headache, parasympathetic, sympathetic, vasoactive intestinal polypeptide*

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Introduction

Autonomic disturbances—namely lacrimation, conjunctival injection, nasal congestion and secretion, facial sweating, eyelid swelling, miosis and ptosis—feature so frequently and prominently during attacks of cluster headache that they form part of the diagnostic criteria for this disorder (1). Lacrimation and nasal secretion are probably due to massive trigeminal-parasympathetic discharge (2–4). In a subgroup of patients the pupil constricts and the eyelid droops on the painful side, both classic signs of ocular sympathetic paralysis (2, 3). The persistence of these ocular signs between attacks and sometimes even between bouts (5–9) implies that cervical sympathetic fibres have been injured. Since thermoregulatory facial sweating and flushing are also mediated by sympathetic neural discharge (10), it is not surprising that these responses are compromised on the symptomatic side of the forehead in

cluster headache patients with signs of oculosympathetic deficit (9, 11). Paradoxically, however, sweating increases on the painful side of the forehead during attacks (12) and blood flow increases substantially around the painful eye (13), implying that a pathological mechanism evokes these responses.

The present review addresses the following points:

- A peripheral rather than a central lesion produces signs of cervical sympathetic deficit in patients with cluster headache.
- Trigeminal-parasympathetic discharge triggers increases in facial blood flow during attacks.
- Supersensitivity to parasympathetic neurotransmitters, together with release of sympathetic vasoconstrictor tone, boosts facial flushing during attacks in patients with cervical sympathetic deficit.
- Parasympathetic rather than sympathetic neural discharge provokes excessive facial sweating during attacks in patients with cervical sympathetic deficit.

Involvement of the cervical sympathetic pathway in cluster headache

Hypothalamic and brainstem neurons that control sympathetic activity in the face synapse with preganglionic sympathetic neurons in the upper part of the spinal cord. Most preganglionic pupillary fibres leave the spinal cord through the first thoracic root, whereas sudomotor and vasomotor fibres leave below this level. The preganglionic fibres then ascend to synapse with postganglionic sympathetic neurons in the superior cervical ganglion. Postganglionic fibres to the eyes and forehead form a plexus around the internal carotid artery, whereas fibres to lower parts of the face follow the external carotid artery. These fibres periodically leave the blood vessels to join peripheral nerves that project to target tissues.

This anatomical arrangement means that injury at different sites produces distinct patterns of autonomic disturbance. For example, an injury to central sympathetic neurons that project to the Edinger-Westphal nucleus in the brainstem (14), or to preganglionic sympathetic fibres in the first thoracic root, generally disrupts ocular sympathetic activity but does not affect vasomotor or sudomotor reflexes in the face (10, 15). Similarly, a paratrigeminal lesion in the middle cranial fossa that disrupts oculosympathetic outflow would spare sudomotor fibres that have already left the internal carotid plexus to join the ophthalmic nerve (16). Conversely, a lesion below the first thoracic root may interrupt sweating and flushing on one side of the face but generally spares pupillary reflexes. This pattern of autonomic deficit is seen after sympathectomy at the $T_{2\text{-}3}$ level (15, 17) and in patients with harlequin syndrome (18). Injury to the plexus around the internal carotid artery inhibits ipsilateral pupillary reflexes and thermoregulatory responses in the medial part of the forehead but not in lower parts of the face, whereas injury proximal to this point blocks sympathetic activity on the entire side of the face and the ipsilateral upper limb (10, 19–21). This helps to narrow down the site of sympathetic lesion in cluster headache, because sudomotor and vasomotor disturbances appear to be greatest in the upper half of the face in patients with ocular signs of sympathetic deficit (5, 9, 11). Moreover, sweating and vascular responses are symmetrical in the hands of cluster headache patients (12, 22), seemingly ruling out a lesion proximal to the superior cervical ganglion. In sum, the sympathetic lesion in cluster headache appears to involve the intracranial part of the cervical sympathetic pathway, most likely in the cavernous sinus region or carotid canal.

Ocular sympathetic deficit

Most studies of ocular sympathetic deficit in cluster headache concur that postganglionic sympathetic neurons are compromised. In patients with clear signs of ocular sympathetic deficit, and even in some with no obvious deficit, pupillary dilation to substances such as tyramine and hydroxyamphetamine is reduced on the symptomatic side (5, 6, 8, 9, 17). Since these substances release noradrenaline from postganglionic sympathetic neurons, diminished pupillary dilation implies that adrenergic stores are low and that at least some of the neurons are injured or dead.

Although attacks of cluster headache almost always affect just one side of the head, they occasionally switch sides between bouts or even within the same bout (23, 24). In such cases, it is not surprising to find evidence of ocular sympathetic deficit bilaterally or on the side that is currently asymptomatic. However, it has been suggested that ocular sympathetic deficit generally extends to the asymptomatic side in patients with cluster headache. For example, pupillary dilation to corneal stimulation at the patient's pain threshold was found to be attenuated bilaterally during the active phase of the cluster headache cycle, particularly on the symptomatic side (25). These findings were taken as evidence of bilateral (presumably central) sympathetic deficit in cluster headache. However, a decrease in stimulus

intensity may also account for these findings, because the corneal pain threshold fell during bouts; moreover, pupillary dilation varied in proportion to stimulus intensity. In other reports, pupillary dilation to painful stimulation elsewhere in the body was attenuated on the symptomatic side during the cluster period (26), was greater bilaterally in asymptomatic cluster headache patients without signs of ocular sympathetic deficit than in controls (27), or was no different between patients and controls, irrespective of whether patients were in the active phase of the headache cycle or in remission (28). These inconsistent findings may be due, at least in part, to variation among samples in the proportion of patients with signs of ocular sympathetic deficit.

Mechanisms other than ocular sympathetic deficit may also influence pupillary responses in patients with cluster headache. For example, Fanciullacci et al. (29) found that brief electrical stimulation of the infratrochlear nerve induced an ipsilateral, slowly developing, long-lasting, non-cholinergic miosis in control subjects. Miosis also developed on the asymptomatic side in cluster headache patients, but was attenuated on the symptomatic side during bouts. Fanciullacci et al. speculated that the miosis was due to antidromic release of neuropeptides from trigeminal nerve endings; if so, recurrent attacks might deplete neuropeptide stores. Indeed, levels of calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) increase substantially in venous jugular blood during attacks (4). Tassorelli et al. (28) reported that miosis developed bilaterally in controls after several minutes of hand immersion in painfully cold water, and that intramuscular injection of 0.4 mg naloxone, an opioid antagonist, blocked this response. In contrast, miosis did not develop in either eye of patients during the cold-water immersion at any stage of the cluster headache cycle, except in patients who were given the naloxone injection. These findings indicate that cluster headache is associated with altered opioid control of pupillary activity, and suggest that a disturbance in central opioid release disrupts autonomic activity (and possibly also inhibitory pain modulation) in cluster headache patients. The persistence of the opioid disturbance during remission suggests that it might increase vulnerability to bouts of cluster headache, although some other factor must be responsible for actually triggering attacks.

Sympathetic control of facial blood flow

Tonic sympathetic vasoconstrictor discharge normally limits the flow of blood through the facial microcirculation. When this inhibitory effect is removed, increases in cutaneous blood flow are greater in the cheek, nose, lips and ears than in the forehead (30–32). Release of sympathetic vasoconstrictor tone may boost blood flow in and around the symptomatic eye during attacks of cluster headache, because increases in peri-orbital temperature are greatest in patients with signs of ocular sympathetic deficit (3).

Increases in facial blood flow during body heating far outweigh the modest increase in blood flow caused by passive release of vasoconstrictor tone (32) (Fig. 1). This active vasodilator mechanism is thought to involve the release of neurotransmitters from sympathetic nerves that innervate sweat glands and possibly also the blood vessels that supply these glands. Kellogg et al. (33) studied the mechanism of this thermoregulatory response in the forearm of healthy human subjects. Atropine pretreatment blocked increases in cutaneous blood flow provoked by the local administration of acetylcholine (indicating that the only functional vascular receptors for acetylcholine were muscarinic).

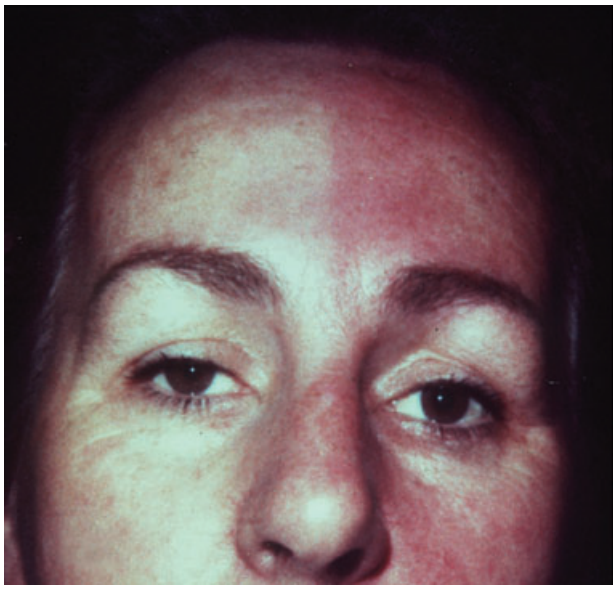

Figure 1 Effect of a preganglionic cervical sympathetic lesion on thermoregulatory facial flushing. Preganglionic sympathetic neurons on the right side of the neck were injured during an operative procedure, producing miosis and ptosis. Despite release of sympathetic vasoconstrictor tone, the right side of the face remained relatively pale during body heating compared with the left. This indicates that the operative procedure interrupted an active sympathetic vasodilator mechanism that mediates thermoregulatory facial flushing. The active vasodilator mechanism appears to involve vasoactive intestinal polypeptide, histamine and nitric oxide. Reproduced by permission of Oxford University Press from Drummond and Lance (10).

Increases in blood flow during body heating persisted after sweating had been abolished with atropine (indicating that active cutaneous vasodilation did not require activation of muscarinic cholinergic receptors). However, botulinum toxin prevented increases in cutaneous blood flow during body heating (indicating that a substance released from cholinergic neurons promoted active cutaneous vasodilation).

Nitric oxide appears to contribute to active cutaneous vasodilation, but does not account completely for this response (34). In particular, microdialysis of the nitric oxide synthesis inhibitor L-NAME in skin pretreated with atropine blunted but did not abolish the increase in cutaneous forearm blood flow during body heating (35). Bennett et al. (36) has recently reported that the VIP analogue VIP_{10-28} attenuated increases in cutaneous blood flow during body heating. In a similar vein, Wong et al. (37) found that antagonism of the H_1 histamine receptor attenuated increases in cutaneous blood flow during body heating. As well as direct actions on vascular VIP receptors, VIP acts on mast cell receptors to release histamine; furthermore, both VIP and histamine stimulate the production of nitric oxide from tissues such as the vascular endothelium which, in turn, relaxes vascular smooth muscle (38). Taken together, these findings suggest that an interaction between VIP, histamine and nitric oxide contributes to thermoregulatory flushing.

Active sympathetic vasodilation is unlikely to mediate increases in facial blood flow during attacks of cluster headache, at least in patients with cervical sympathetic deficit. However, as discussed below, supersensitivity to VIP in this subgroup of patients could boost trigeminal-parasympathetic vasodilation, and may thus contribute to autonomic disturbances during attacks.

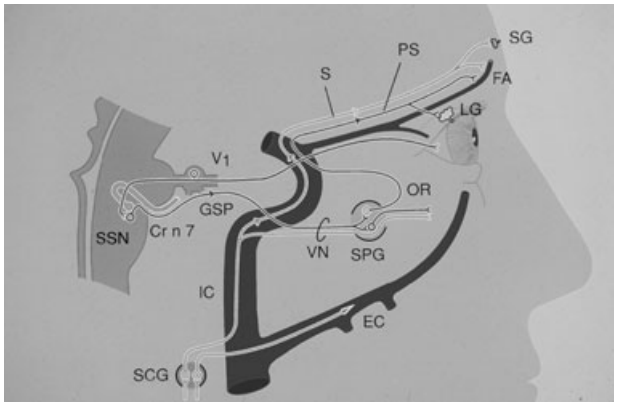

Figure 2 Neural pathway for trigeminal-parasympathetic vasodilation and lacrimation. Trigeminal nociceptive neurons (V_1) supply facial tissues (the eyes, mouth, nose and skin) and intracranial arteries. They relay in the superior salivatory nucleus (SSN) of the brainstem with parasympathetic neurons that emerge from the brainstem in the facial nerve (CrN7) and project through the greater superficial petrosal (GSP) and Vidian nerves (VN) to synapse with postganglionic parasympathetic neurons (P) in the sphenopalatine ganglion (SPG). Postganglionic parasympathetic fibres loop back through orbital rami (OR) to the cavernous sinus before projecting to the lacrimal glands (LG) and nearby blood vessels (FA). Mini-ganglia in the internal carotid canal and cavernous sinus might also supply the internal carotid artery with parasympathetic fibres. The parasympathetic supply to much of the lower part of the face leaves the brainstem with the glossopharyngeal nerve and travels to the otic ganglion, which distributes postganglionic fibres to target tissues in and around the mouth (pathway not shown). Postganglionic sympathetic fibres (S) originate in the superior cervical ganglion (SCG) and form a plexus around the internal (IC) and external carotid arteries (EC) before branching off to join cranial nerves. They ultimately supply facial sweat glands (SG) and arterioles (FA). Sympathetic and parasympathetic neurons employ vasoactive intestinal peptide and nitric oxide to dilate blood vessels. Sympathetic fibres that follow the internal carotid artery through the carotid canal may be compressed when the blood vessel swells during attacks of cluster headache. Collateral sprouts from parasympathetic fibres then grow into vacated sympathetic pathways and make functional connections with sweat glands and blood vessels in the forehead. Reproduced by permission of Oxford University Press from Drummond and Lance (10).

Trigeminal-parasympathetic involvement in cluster headache

Painful stimulation of the eyes, mouth, nose and facial skin triggers parasympathetic reflexes, resulting in vasodilation, lacrimation, rhinorrhoea and salivation. Trigeminal nociceptive neurons that supply intracranial arteries and facial tissues relay in the brainstem with parasympathetic neurons that travel with the facial and glossopharyngeal nerves to the sphenopalatine and otic ganglia (Fig. 2). Postganglionic parasympathetic fibres innervate facial glands, the blood vessels of these glands, the cutaneous microvasculature surrounding the eyes and mouth, and large intracranial arteries. In humans, injection of capsaicin into the skin of the forehead provokes pain and dilation of the internal carotid artery above the level of the internal carotid siphon, similar to changes noted during attacks of cluster headache (39). These findings complement experimental studies in animals, which demonstrate that nociceptive stimulation of cranial tissues provokes trigeminal-parasympathetic vasodilation in the intracranial circulation (40).

Like the active sympathetic vasodilator mechanism, parasympathetic vasodilation is mediated by

VIP and nitric oxide (41, 42). This increases the prospect that collateral parasympathetic fibres make functional connections with sympathetically denervated VIP receptors after injury to sympathetic fibres. As discussed below in the section on pathological sweating and flushing, this process could contribute to autonomic disturbances in cluster headache.

Levels of the powerful neuropeptide vasodilator CGRP increase in jugular venous blood during attacks of cluster headache (4). Similarly, levels of CGRP rise in jugular venous blood during thermocoagulation of the trigeminal ganglion (43), presumably due to antidromic discharge of trigeminal sensory afferents and release of CGRP from peripheral nerve terminals. During trigeminal thermocoagulation, flushing develops in the cutaneous distribution of the division being coagulated (44). This flush is associated with an increase in facial blood flow and temperature (45), similar to changes observed during attacks of cluster headache (13, 46). The flush during trigeminal thermocoagulation (45) and cluster headache (13) spreads well away from the forehead and mouth, i.e. well outside the distribution of trigeminal-parasympathetic vasodilator reflexes (47, 48). Trigeminal neurogenic vasodilation probably supplements trigeminal-parasympathetic vasodilation both in the facial microcirculation and in large intracranial vessels during attacks of cluster headache. Moreover, a neurogenic inflammatory response that triggers perivascular oedema might injure sympathetic fibres in the carotid canal during attacks of cluster headache. This possibility is addressed further in the concluding section of this review.

Pathological sweating and flushing

Pathological gustatory sweating and flushing in Frey's syndrome involves the growth of parasympathetic nerve endings into sites previously occupied by sympathetic nerves. As discussed below, a similar mechanism might contribute to facial sweating and flushing during attacks of cluster headache in patients with cervical sympathetic deficit.

Frey's syndrome develops months or years after injury to a branch of the mandibular nerve that interrupts the sympathetic supply of blood vessels, sweat glands and salivary glands within the distribution of that nerve branch. Parasympathetic fibres supply the parotid gland and other salivary and mucous glands with secretomotor fibres, and also supply the vasculature of the glands and oral region with vasodilator fibres. Frey's syndrome appears to involve misdirected regeneration or collateral sprouting of parasympathetic fibres into vacated sympathetic pathways. Over time, functional connections develop between parasympathetic secretomotor and vasodilator fibres and sympathetically denervated sweat glands and cutaneous blood vessels, presumably because similar substances are employed as neurotransmitters. Consequently, parasympathetic discharge provokes flushing and sweating in sympathetically denervated skin, probably by exciting sensitized VIP receptors.

More than 20 years ago, VIP was identified as the probable mediator of vasodilation in salivary and lacrimal glands (41) and possibly also sweat glands (49), which are surrounded by a dense network of VIP-immunoreactive nerve fibres (50). Nitric oxide appears to regulate both the release of VIP from parasympathetic nerves and postjunctional vascular reactivity to VIP (42). VIP has been detected in cranial parasympathetic ganglia (51), and nerve fibres containing VIP and nitric oxide synthase congregate around large proximal arteries that supply muscles, glands, the supraorbital skin and the mucous membranes of the face (52). Thus, the release of VIP and nitric oxide from collateral sprouts of parasympathetic fibres could contribute to pathological gustatory flushing and sweating by acting on receptors that previously mediated sweating and active sympathetic vasodilation in the facial skin.

Although thermoregulatory flushing and sweating are impaired on the symptomatic side of the forehead in cluster headache patients with ocular signs of sympathetic deficit (9), sweating and blood flow often increase in this part of the forehead during attacks (12, 13, 46). In fact, the increase in periorbital blood flow during attacks of cluster headache is greatest in patients with profuse lacrimation and ocular sympathetic deficit (3), suggesting some parallels between these autonomic disturbances and Frey's syndrome. In support of this notion, painful stimulation of the eye provoked sweating and increases in blood flow on the sympathetically denervated side of the forehead in cluster headache patients with ocular signs of sympathetic deficit, and in patients with a postganglionic sympathetic lesion from some other cause (Table 1). Even contralateral eye pain provoked sweating on the sympathetically denervated side of the forehead in patients with a postganglionic lesion (17). In contrast, minor facial sweating to eye pain was symmetrical in most patients with a central or preganglionic sympathetic lesion (Table 1).

The most straightforward explanation for pathological lacrimal sweating and flushing is that parasympathetic lacrimal and vasodilator fibres make

Table 1 Prevalence of lacrimal sweating in patients with cervical sympathetic deficit

	Lacrimal sweating[a]	
	Present	Absent
Central sympathetic lesion	0	3
Preganglionic lesion	1	10
Postganglionic lesion (7 with cluster headache)	13	0

[a]Sweating was provoked in the sympathetically denervated region of the forehead by painful stimulation of the eye (17).

functional connections with VIP receptors previously supplied by sympathetic sudomotor and vasodilator nerves. In this scenario, trigeminal-parasympathetic discharge to the lacrimal glands would also trigger sweating and flushing in sympathetically denervated parts of the forehead. It is noteworthy that levels of VIP increase substantially in jugular venous blood during attacks of cluster headache (4), consistent with massive trigeminal-parasympathetic discharge.

The forehead sweat glands of cluster headache patients are supersensitive to cholinergic substances (11), as are the sweat glands of at least a subgroup of patients with postganglionic cervical sympathetic deficit from some other cause (53). This supersensitivity may enhance pathological lacrimal sweating to eye pain, and sweating during attacks of cluster headache. Sympathetic denervation boosts the vasodilator response to eye pain, irrespective of the site of lesion in the cervical sympathetic pathway (17). This vascular supersensitivity (presumably to VIP) could enhance trigeminal-parasympathetic vasodilation during attacks of cluster headache in patients with sympathetic deficit.

Possible mechanisms of autonomic disturbance in cluster headache

As outlined above, neurogenic vasodilation and trigeminal-parasympathetic discharge during attacks of cluster headache could trigger glandular secretions, increase blood flow around the affected eye and induce vasodilation of large intracranial arteries. Pain generally precedes autonomic disturbances during attacks and escalates within a few minutes from a niggling sensation to intense pain (13). Thus, recruitment of secondary autonomic disturbances may cause pain to build up in a positive loop. A working model of this process is described below.

The intracranial segment of the internal carotid artery is supplied by parasympathetic fibres that originate in mini-ganglia in the carotid canal and cavernous sinus, and by trigeminal sensory fibres that pass through or synapse in these ganglia (54). An inflammatory process that excites these pericarotid trigeminal nociceptors might trigger neurogenic inflammation and trigeminal-parasympathetic dilation of the internal carotid artery in cluster headache (54, 55). Since mast cells have receptors for neuropeptides, release of CGRP and VIP during trigeminal-parasympathetic discharge could liberate mast cell products that aggravate inflammation and intensify trigeminal discharge. The vicious circle between autonomic disturbances and pain may continue until mast cell products are depleted, trigeminal discharge is suppressed by an endogenous pain control mechanism, or the trigeminovascular response fatigues.

Although it would be difficult to investigate intracranial mast cell populations in cluster headache patients, mast cells in skin biopsies taken from the temples show signs of increased degranulation (56–58). It is interesting to note that sympathetic vasoconstrictor activity suppresses neurogenic vasodilation (59), and that catecholamines inhibit mast cell degranulation (60); thus, release of sympathetic vasoconstrictor tone in patients with cervical sympathetic deficit could enhance vasodilation and promote the release of mast cell products. Cervical sympathectomy increases mast cell density and histamine content in the rat dura mater, possibly because of increased production of nerve growth factor in sympathetically denervated tissues (61). Thus, cervical sympathetic deficit may cause mast cells to congregate around cranial blood vessels in cluster headache.

Many years ago, Gardner et al. (62) demonstrated that surgical resection of parasympathetic fibres in the greater superficial petrosal nerve prevented lacrimation during attacks of cluster headache. If peripheral trigeminal nociceptor discharge triggers this parasympathetic reflex, then trigeminal blockade or surgical resection of the trigeminal root should also prevent lacrimation during attacks. However, cyclical parasympathetic disturbances with or without headaches occasionally persist after trigeminal surgery (63), suggesting that parasympathetic disturbances might be triggered centrally during attacks of cluster headache, and not necessarily by trigeminal activity. In addition, cyclical autonomic dysfunction without headache occasionally precedes (64) or follows typical bouts of cluster headache (65). Although such observations suggest

that a central generator (e.g. in the hypothalamus) triggers pain and autonomic disturbances independently, a peripheral stimulus (e.g. an infection or allergy) could also provoke episodic autonomic disturbances without pain in physiologically primed tissues. Sweating, lacrimation and nasal secretions increase slightly on the pain-free side during attacks of cluster headache (66), implying the involvement of centrally mediated reflexes. However, this does not necessarily implicate a central generator, because peripheral nociceptive stimuli provoke weak contralateral parasympathetic responses (47, 67) due to minor crossover of trigeminal-parasympathetic reflexes in the brainstem.

As summarized in Table 2, several lines of evidence point to a lesion of postganglionic sympathetic fibres in a subgroup of cluster headache patients. Within this subgroup, parasympathetic discharge may trigger pathological facial sweating and vasodilation during attacks. It is interesting to note that pathological gustatory sweating is sometimes painful (68, 69), implying that parasympathetic discharge can stimulate nociceptors (e.g. by increasing production of endothelial nitric oxide, by degranulating mast cells, or by direct cross-excitation of nociceptive afferents). It is tempting to speculate that parasympathetic discharge during attacks of cluster headache provokes pain in patients with cervical sympathetic deficit, both within intracranial vessels and within the facial microcirculation.

Ekbom and Grietz (70) observed dilation of the ophthalmic artery in a patient who developed an attack of cluster headache while undergoing carotid angiography. Local narrowing of the extradural part of the internal carotid artery spread into the carotid canal as the attack progressed, consistent with oedema in the arterial wall. Notably, this patient had ocular signs of sympathetic deficit. In contrast, dilation of the ophthalmic artery without internal carotid artery narrowing or ocular signs of sympathetic deficit was detected by magnetic resonance angiography in another patient during two spontaneous attacks (71). These observations support the notion that perivascular oedema in the carotid canal during attacks of cluster headache injures the pericarotid plexus of sympathetic nerve fibres, perhaps due to nerve compression (54). Alternatively, an inflammatory process in the cavernous sinus that blocks venous drainage may damage pericarotid sympathetic fibres (55). Consistent with these proposals, dilation of the common carotid artery during head-down tilt sometimes provoked ocular sympathetic deficit and intense headache during the active phase of the cluster headache cycle (72).

In conclusion, trigeminal-parasympathetic discharge and sympathetic deficit probably do not trigger attacks of cluster headache. Nevertheless, once the attack begins, these autonomic disturbances may contribute to the rapid escalation of pain. Attacks are thought to be initiated by hypothalamic discharge (40, 73), but what triggers this hypothalamic discharge is unknown. One possibility is that a recurrent infection that produces inflammation and vascular disturbances in the carotid sinus (55) disrupts the blood supply of the hypothalamus (74). If so, attacks of cluster headache could represent a recurrent but futile attempt to clear away a source of infection that threatens the brain's blood supply.

Table 2 Signs of postganglionic sympathetic deficit in cluster headache

Loss of pupillary dilation to tyramine and hydroxyamphetamine eyedrops
Loss of thermoregulatory sweating and flushing in the forehead
Thermoregulatory sweating and flushing preserved in other parts of the face
Sweating in the forehead to eye pain (lacrimal sweating)
Symmetrical electrodermal and vasoconstrictor responses in the hands

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