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Do changes of ANS in migraine subjects play a pathogenetic role?

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Abstract Migraine, characterized by several autonomic disturbances both during and between attacks, suggests an involvement of the autonomic nervous system (ANS). To clarify the role of the ANS in migraine pathogenesis, we reviewed the major studies on autonomic function. The results of these investigations are contradictory, suggesting hypo- and hyperfunctioning of both the sympathetic and parasympathetic nervous systems.

Key words Autonomic nervous system • Migraine • Pathogenesis

Introduction

The possible involvement of the autonomic nervous system (ANS) in the pathogenesis of migraine has long been a subject of considerable interest: its role has been implicated by several autonomic disturbances both during a migraine attack and interictally.

Migraine has been considered to be a dysautonomia involving mainly the intrinsic noradrenergic nervous system [1]. ANS functions of patients with migraine have been investigated by means of cardiovascular reflexes, pharmacological tests, and pupillometric and biochemical methods. However, the results of these investigations have been contradictory, suggesting both sympathetic hypofunction and hyperfunction in migraine patients.

Cardiovascular reflexes

The autonomic cardiovascular control of patients with migraine, with and without aura, has been investigated in several studies both during the attack and in headache-free intervals. Some authors reported that migraineurs show both sympathetic hypofunction and hyperfunction. Steiner et al. [2] reported that patients with migraine without aura (MwoA) during headache-free intervals have sympathetic hypofunction. Gotoh et al. [3] confirmed this finding by means of Valsalva manoeuvre, a postural test and Aschner's test (inducing reflex bradycardia by pressure on the eyeballs) in patients with MwoA and migraine with aura (MwA) during headache-free intervals. They also performed pharmacological tests by administering noradrenaline (NA) and mea-

suring serum catecholamine levels, and proposed both a sympathetic hypofunction with denervation hypersensitivity and a parasympathetic hyperfunction. An extensive series of studies has been published by Havanka-Kanniainen et al. [4–8]. This group studied young migraine patients with and without aura (aged 11–22 years). None of the young patients had any symptoms suggesting autonomic disturbance during headache-free intervals, but some of the older patients reported mild symptoms with a sympathetic hyperfunction; during migraine attack they also showed a blood pressure (BP) reduction in the isometric work test. The R-R interval ratio values were also significantly lower during normal and deep breathing and in the Valsalva manoeuvre, suggesting a parasympathetic hypofunction.

Mikamo et al. [9] supported sympathetic hypofunction in migraineurs during headache-free intervals in a study of cardiovascular reflexes and plasma levels of NA. Their observations indicated a remarkable BP reduction after tilting in patients with MwoA and MwA compared with healthy controls. Plasma NA levels were reduced in migraineurs. Other investigators [10] also reported sympathetic hypofunction in patients during headache-free intervals, finding a pressor hyperresponsiveness to phenylephrine, a reliable index of hypersensitivity of vascular adrenergic receptors that is compatible with the presence of a chronic adrenergic deficit in migraineurs. Martin et al. [11] found a reduction of heart-rate (HR) response during deep breathing, and a remarkable reduction of BP and HR response after two minutes of tilting. The authors found no differences between migraineurs with and without aura and described normal responses to other cardiovascular tests; they suggested hypofunction of the ANS primarily involving the sympathetic system.

Recently, Pogacnik et al. [12] found a reduced HR increase in migraineur patients with normal pressure response during sustained muscular strain (sustained handgrip test). They suggested a sympathetic hypofunction instead of the normal tests results. Drummond [13], in contrast to previous authors, hypothesized a sympathetic hyperfunction after finding a remarkably increased amplitude of temporal artery pulse rate and increased breath rate, BP and HR during situational stress in a headache-free interval in migraineurs with aura. In a recent study using power spectral analysis to investigate the autonomic control of HR variability over 24 hours in migraineurs patients [14], some authors found an increase in fluctuation of the low-frequency band, corrected by verapamil; this study suggests an increased sympathetic vasomotor control without an associated reduction of parasympathetic response. Results obtained by Thomsen et al. [15] suggested a preserved sympathetic functionality and found no differences between migraineurs, even during the attack, and healthy control subjects, regarding head-up tilt test and cold pressor test response. They hypothesized a mild parasympathetic hypofunction after they found a reduced Valsalva ratio in patients with MwoA and MwA.

In a pharmacological, biochemical and physiological study [16], we showed an aspecific sympathetic hyperactivity. HR was higher in migraineurs than in the control group. BP during cold-face test and isometric handgrip test showed a remarkable increase in the same group of patients. However, these results did not confirm an autonomic cardiovascular dysfunction in patients with MwA.

Recently, we studied a large sample of MwoA and MwA patients using a power spectral analysis of HR and diastolic blood pressure (DBP) variability in both supine and orthostatic conditions [17]. The study showed a normal vagal-sympathetic interaction of the autonomic control of the cardiovascular system; cardiovascular responses to the head-up tilt test and to Valsalva manoeuvre showed a normal function of the overall baroreceptor reflex arc. Finally, normal HR responses to Valsalva manoeuvre and deep breathing suggested an intact parasympathetic function.

Vasomotor reactivity

Many studies regarding peripheral vasomotor, retinic and cerebrovascular reactivity have been performed in patients suffering from migraine but the results have been contradictory. Some authors disclosed a reduced peripheral vasodilatation in response to calories test in migraineurs during headache-free intervals [18, 19]. Furthermore, Downey and Frewin [20] found a decrease of peripheral vasoconstriction after cold test. Other studies concluded for a normal vasomotor-reflex response in migraine [21, 22]. Gomi et al. [23] studied retinal vasomotor reactivity during head-up tilt test in the interictal phases of migraineurs with and without aura and showed a sympathetic hypofunction. A study using transcranial Doppler showed a reduction of blood flow in the medial cerebral artery (MCA) unilateral to pain during migraine attack, suggesting an abnormal dilatation [24, 25]. However, Thomsen et al. [15] showed no differences between migraineurs, either during or between attacks, and a healthy control group regarding blood flow of MCA in responses to head-up tilt test, cold pressor test and Valsalva manoeuvre.

Pupillometry

Pupillometric studies in migraineurs have been contradictory, suggesting a sympathetic hypofunction. Fanciullacci [26] observed reduced mydriasis induced by fenfluramine and a wider and prolonged myosis in response to guanethidine drops in patients with MwoA, during headache-free intervals, compared to a healthy control group. He hypothesized a reduced concentration and synthesis of NA in presynaptic

pupillary terminals. In addition, he found an increase of NA-induced mydriasis, suggesting a denervation hypersensitivity of α-adrenoceptors.

Sympathetic hypofunction was demonstrated in patients with MwoA and MwA in studies using pupillary reaction to cocaine [27], during attacks or in headache-free intervals, and to epinephrine [3]. Rubin et al. [28] found a phasic hyperfunction of sympathetic innervation of the pupil in response to the cold-pressor test in interictal phases of MwoA.

Micieli et al. [29], in contrast to other authors, obtained different results indicating both a sympathetic hyperfunction and a parasympathetic hypofunction in subjects with MwoA and MwA during headache-free intervals. They studied pupillary diameter variations in different experimental situations (dark-light adaptation, light reflex, sural nerve stimulation) using TV pupillometry and found a wider pupil after light and dark adaptation and a contraction and redilatation time shorter to bright stimulus.

Drummond [30] used pupillometric test and thermography, and suggested the presence of a generic sympathetic hyper- and hypoactivity dysfunction in migraineurs. In a previous study Balottin et al. [31] showed a normal functionality of sympathetic pupillary in paediatric patients with migraine.

Biochemical studies

To ascertain the involvement of the sympathetic system in the pathogenesis of migraine, different authors measured plasma catecholamines levels and their metabolites and urinary secretion. Some authors revealed an increase in venous NA [32] and adrenaline [33] during the attack and in headache-free intervals. Other authors found the same parameters (adrenaline, venous and arterial haematic NA) to be reduced [3, 34]. Fog-Moller et al. [35] found a normal venous adrenaline concentration and a reduction of NA during the attacks. Schoenen et al. [36], on the other hand, reported a normal venous adrenaline concentration and an increase in NA in headache-free intervals.

D'Andrea et al. [37] measured platelet NA, adrenaline and dopamine levels in a group of patients with MwoA during the interictal phase after 1 and 30 minutes of supine rest. Their findings supported the hypothesis of sympathetic hypofunction in migraine. Takeshima et al. [38] reported the same conclusion after measuring plasma platelet factor 4 and platelet NA in patients with MwoA and MwA in basal conditions and during the cold-pressor test. Other authors [34, 39] found an increase in dopamine β-hydroxylase activity in venous blood of migraineurs during and between attacks and suggested a sympathetic hyperfunction. Urinary excretion of vanillymandelic acid, a reliable index of sympathetic activity, has been found both increased [40] and normal [41] during migraine attacks.

Other biochemical studies revealed an increase in plasma cAMP concentration during and between migraine attacks [34, 42] and showed a significant increase in cGMP after administration of metacholine, an index of a parasympathetic denervation hypersensitivity [43]. In conclusion, the interaction between the noradrenergic system and the central serotoninergic system supports the hypothesis that platelets release serotonin (5-HT) during migraine attacks and that there is an increase in metabolic turnover of 5-HT in interictal periods [44]. It is unclear how this may modify ANS functionality in migraineurs.

Miscellaneous

Gomi et al. [23] studied thermoregulation in migraineurs by measuring the sweating function of patients with MwoA and MwA after administration of pilocarpine. Their results suggested a sympathetic hypofunction in patients with MwA during headache-free intervals. Fagius [45] observed normal muscle nerve sympathetic activity in migraineurs. Recently, Evers et al. [46] evaluated sympathetic skin responses in patients with different kinds of headaches including migraine, and observed an increase in latencies, an index of a common sympathetic hypofunction in different headaches. In this study, migraineurs with a high frequency of attacks had normal latencies. Drummond [47] tested the integrity of facial parasympathetic reflexes in patients with MwoA and MwA during the interictal period, studying vascular and lacrimal responses to painful mechanical and visual stimulations. He showed that light-induced pain increased during mechanical and bright light stimuli, and that mild trigeminal-parasympathetic reflexes deficit a reduced tolerance to painful mechanical and visual stimulation. The author hypothesized that migraine is associated with a loss of inhibitory subcortical processes which normally suppress sensation of glare and light-induced pain, and which normally suppress the intensification of these sensations in the presence of facial pain.

Conclusions

The results of investigations on ANS function in different structures have been contradictory and difficult to explain. They may be partly due to procedural discrepancies or possibly reveal an effective heterogeneity in ANS function in the migraineur population. This suggests that an altered tone of ANS is unlikely to be the threshold for migraine activation. However, the ANS may play a role in characterizing "migraine brain"; that is still unsettled.

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