SHORT REPORT

Catecholamine levels in plasma and CSF in migraine

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Abstract
There is clinical and pharmacological evidence of the existence of sympathetic dysfunction in migraine. Adrenaline and noradrenaline concentrations were determined in plasma and CSF of patients during attacks of common or classic migraine, comparing them with controls suffering from stress. Plasma noradrenaline levels were significantly lower in the patients with common migraine than in controls (p < 0.05). Other catecholamine levels in plasma and CSF in both migraine groups were only slightly lower than in controls. Our results suggest that central sympathetic dysfunction exists in patients with migraine.

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The mechanism of pain and vascular changes in migraine is unknown. There is evidence that central monoaminergic systems are altered before and during attacks. Recent hypotheses propose that central catecholaminergic pathways play a role in migraine. Potentiators of the migraine attack may lower the threshold of the orbitofrontal-brainstem projections that influence the intrinsic noradrenergic system.1

Electrophysiological,2 clinical,3 and pharmacologic4 studies suggest central and peripheral sympathetic hypofunction in migraine. Abnormal reflex responses demonstrating this deficit correlate well with low noradrenaline levels.5 Biochemical data have been conflicting, showing high6, normal7 or low8 levels of catecholamines in body fluids. Little is known about catecholamine levels in CSF in migraine. We have measured adrenaline and noradrenaline concentrations in patients with common and classic migraine during crises, comparing them with control subjects suffering from physical or psychological stress.

Material and methods
SUBJECTS
Patients were studied in the headache unit of the neurology department of Galicia General Hospital, Santiago de Compostela University, Spain. Informed consent was obtained from subjects after explanation of the procedures. We included 16 patients with common migraine, 11 with classic migraine, and 21 controls. Diagnosis of common or classic migraine was made following criteria of the headache classification committee of the International Headache Society.7 The control group was composed of patients suffering physical or psychological stress, with the following diseases: patients immediately before surgical intervention (n = 9), multiple sclerosis (n = 2), acute stroke during the 24 first hours (n = 8), Guillain-Barré syndrome after the acute phase (n = 1), and lymphoma (n = 1). Exclusion criteria for patients and controls were hypertension, psychiatric disease, epilepsy, and intake of antidepressive and adrenergic drugs or calcium channel blockers. Smokers were excluded. Controls with abnormalities in CSF (cell count, and protein and glucose content) were excluded. Mean ages (SD) of common and classic migraine patients and controls were 38-37 (11.7), 39 (11.03) and 49-95 (11.40) years. The male/female ratios of the three groups were 0.33, 0.57, and 1.62. Duration of migraine history was 19-43 (10-26) years in common migraine and 12-72 (5-46) in classic migraine. Severity of headache was evaluated by the score units measure (SUM), expressed in headache units, according to international criteria.8 Duration of crisis was recorded as the time from onset of headache until sample extraction.

ANALYTICAL METHOD
Blood collected by venepuncture after 30 minutes' rest in supine position was centrifuged (3000 g for 15 minutes). Lumbar puncture was performed with patients in left lateral decubitus after 30 minutes' rest. Initial pressure was measured and 5 ml of CSF were discarded. The sixth ml was used for cell count and protein and glucose analysis. The next 5 ml of CSF were centrifuged (2000 g for 10 minutes) and used for catecholamine assay. Plasma and CSF samples were stored (−70°C). Extractions were performed between 9 and 10 am in controls after an 8 hours fast. In patients with migraine extractions were carried out at variable hours, during an attack and after a minimum 4 hours fast. Measurement of catecholamines was performed using high pressure liquid chromatography with electrochemical detection.
Mean level

Figure 2 Adrenaline (○) and noradrenaline (●) concentrations in plasma (pg/ml). Mean level (−).

Figure 3 Adrenaline (○) and noradrenaline (●) concentrations in CSF (pg/ml). Mean level (−).

Discussion

Monoamine levels in CSF and plasma may reflect monoaminergic activity. We have measured catecholamine levels in plasma and CSF of patients with common and classic migraine during attacks using HPLC-EC. Variability of interlaboratory results depend on the sensibility of the method, and the interference of acid or oxidizing substances. This problem has occurred with a proportion of samples in our study.

Important variability of results was...
observed. Levels in CSF were lower than in plasma for both catecholamines in the three groups. We have standardised as many external potential factors that influence sympathetic function as possible. Plasma and CSF levels have been lower than those previously reported in resting controls. Mean catecholamine levels in plasma or CSF were lower in migraine groups than in controls. Differences were not statistically significant except when comparing noradrenaline levels in plasma between common migraine patients and controls (p < 0.05). Our results may suggest that during migraine attacks catecholamines are defective released, although further studies are required. Though precise location of the defect cannot be determined, results in plasma and CSF suggest both a central and peripheral deficit. We observed correlation between adrenaline levels in CSF and severity of headache in patients with classic migraine.

Previous reports of catecholamine levels in migraine have been conflicting. CSF studies have focused upon catecholamine metabolites. Lower levels than in healthy controls have been reported, during and between crisis. Biochemical data correlate with clinical studies that demonstrate sympathetic dysfunction. The mechanism by which this dysfunction may participate in the physiopathology of migraine remains elusive. Indirect evidence shows that the noradrenergic system represents the threshold for the attacks. Potentiators of migraine probably modulate sympathetic activity. Clinical and biochemical results suggest that migraine patients have an abnormal adaptative reaction to stress. Central noradrenergic systems modulate nociceptive transmission to the central nervous system. Their dysfunction may cause perturbation of these pain modulating systems. Also, these cerebral pathways participate in the regulation of cortical blood flow. Chronic sympathetic hypofunction may lead to denervation supersensitivity of cerebral vessels. Triggering factors may then cause overconstriction, promoting the vascular phenomena observed in migraine.
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