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REVIEW ARTICLE

The role of neurotransmitters and neuromodulators in the pathogenesis of cluster headache: a review

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Abstract
The pathogenesis underlying cluster headache remains an unresolved issue. Although both the autonomic system and the hypothalamus play a central role, the modality of their involvement remains largely unknown. It is, also, unknown why the duration of the pain attacks is so brief and why their onset and termination are abrupt and extremely painful. This review summarizes the evidence to date accumulated in favor of a possible role of anomalies in the metabolism of tyrosine, tryptophan, and arginine in these unresolved issues.

Keywords Cluster headache · Tyramine · Tryptamine · TAARs · NO

Introduction

Cluster headache (CH) is a trigeminal autonomic cephalalgia (TAC) characterized by severe, excruciating, unilateral headache attacks. In accordance with the HIS classification, CH is clinically present in two forms: episodic and chronic. In episodic CH, periodic pain attacks last for weeks or months (active period), with attacks subsiding in the headache-free remission periods. In the chronic form (CCH), the pain attacks are continuous for at least 1 year from the onset of the symptomology [1]. The episodic form may become chronic: this occurs when the length of the time interval between two active periods disappears over time. The fact that autonomic signs such as restlessness, miosis, ptosis, lacrimation, nasal stiffness along with secretion, and sweating always accompany CH attacks suggests that dysfunction of both the hypothalamus and autonomic system is involved. However, to date, the causes remain unknown [2].

We here describe the biochemical anomalies in the metabolism of tyrosine (Tyr) and tryptophan (TPR) as well as that of Tyr, TPR, and arginine (A) in patients suffering from episodic CH and CCH, respectively. The diagnosis was made in all patients according to ICHD-3 beta criteria.

Tyrosine metabolism in episodic CH

Studies published in last decade raise the possibility that anomalies in Tyr metabolism may play a role in the pathogenesis of CH [3, 4]. Tyr is the substrate for the synthesis of catecholamines and elusive amines. The Tyr hydroxylase enzyme transforms Tyr in dopamine (DA) and noradrenaline (NE), whereas the Tyr decarboxylase enzyme is involved in the synthesis of the elusive amines, such as tyramine (Tyra), octopamine (Oct), and synephrine (Syn). Both enzymes are regulated by mitochondrial activity. In conditions of low mitochondrial function, the activity of the decarboxylase enzyme increases, whereas that of the hydroxylase enzyme decreases [5, 6].

The elusive amines, similar in structure to NE, play a significant role in synaptic transmission, acting as neuromodulators within the central nervous system (CNS). The neuromodulators, released from the cell, act to modify the action (increasing or decreasing) of coexisting neurotransmitters (DA, NE). When alone, however, they do not change the excitability of the postsynaptic neuron [7, 8].

Trace amine–associated receptors (TAARs) represent a family of G protein–coupled presynaptic inhibitory receptors activated by elusive amines [9]. $TAAR_1$, the most abundant receptor subtype, is widely distributed in many subcortical centers including the hypothalamus and connected structures

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(amygdala, limbic system, and centers of the pain matrix) where they modulate the release of DA and NE [10].

Based on the above, we hypothesized that a shift of Tyr metabolism resulting in an increase of elusive amines and reduction of NE may contribute to the pathogenesis of CH. To demonstrate this hypothesis, we measured catecholamines along with the different products of TYR metabolism in CH patients in numerous studies.

Catecholamines

The first demonstration that anomalies in catecholamines occur in CH patients derives from the measurement of the circulating platelet levels of DA and NE in both remission and active periods. Platelets were employed because they take up and store circulating catecholamines and the other amines in dense bodies for 2 weeks and represent a model to study their metabolisms over time [11]. The platelet levels of DA, amine that derives from the decarboxylase of DOPA, were significantly more elevated in CH patients, particularly in the active periods [12]. On the contrary, the levels of NE were significantly lower in the platelets of the patient cluster groups. All this led to the suggestion that anomalies that NE may play a role in the dysfunction of the autonomic system and hypothalamus characterizing CH [13, 14].

Elusive amines

Utilizing a new HPLC method, we measured the levels of Tyr, Oct, and Syn in plasma and platelets of the two groups of episodic CH patients in the remission and in the active periods. In comparison with control subjects, all three elusive amines were found several folds higher in plasma and platelets in both groups of patients. In comparison with the remission group, the levels of the amines were significantly more elevated in the patients in the active periods [15, 16] (Tables 1 and 2). These results support the above hypothesis that an increase in tyrosine decarboxylase activity results in elevated levels of elusive amines (neuromodulators) along with lower levels of NE (neurotransmitter). This abnormality characterized by an imbalance between neuromodulators and neurotransmitters may have impact on the pathogenesis of CH should the same abnormal scenario occur in the CNS [17].

Indoles

TPR is the amino acid precursor of 5-HT, synthesized via the TPR hydroxylase enzyme, and the end product 5-hydroxyindoleacetic acid (5-HIAA). The serotoninergic system plays a pivotal role in the regulation of the pain threshold, acting on the brain stem nuclei that discriminate and modulate the incoming pain sensations from the spinal cord [18]. In order to evaluate the role of the indoles in CH, 5-HT and 5-HIAA were measured in plasma of a group of episodic CH patients. Plasma levels of both 5-HT and 5-HIAA were found to be significantly more elevated in the patients with respect to healthy controls. These results suggest, again if the plasma levels reflect those in the CNS, that the serotoninergic system is activated in CH and may play a role in the pathogenesis of CH [19] .

Tyrosine metabolism in CCH

The pathogenesis underlying the chronicity in episodic CH is unknown as is the pathogenesis of CCH itself. Whether the anomalies in the synthesis of catecholamines and elusive amines, found in episodic CH patients, play a role in the pathogenesis of CCH is also unknown. We therefore conducted a study evaluating the different products of tyrosine metabolism in a group of CCH patients, a group of CCH patients evolved from episodic form, and control subjects. DA and NE were measured in plasma in all groups of subjects. The plasma levels of DA were found, as in episodic CH, several folds higher in CCH patients with respect to controls. In contrast to patients with episodic CH, NE plasma levels were found highly elevated in CCH patients. The plasma levels of DA and NE were similar in CCH and CCH patients evolved from the episodic form. In comparison with control subjects, all CCH patients were characterized by very high plasma level of Tyr, whereas the levels of Oct and Syn were significantly lower [20] (Table 3).

Tryptophan metabolism CCH

As previously mentioned, TPR is the amino acid precursor of 5-HT and 5-HIAA via the decarboxylation of tryptamine (Try). The role of Try in the CNS was unknown until the discovery that Try is an agonist of 5-HT_{1A} and 5-HT_{2A} receptors and, as such, modulates the pain threshold [21, 22]. This amine acting on 5-HT_{1A} receptors reduces the release of GABA from the inhibitory interneurons of the cortical and subcortical serotoninergic neurons. 5-HT_{2A} receptors, on the other hand, are densely distributed throughout the cortex, including the prefrontal cortex, as well as in the ventral tegmental area, substantia nigra, and striatum. In the orbitofrontal cortex, 5-HT2A induces the excitation of serotonergic neurons connected to the PAG, resulting in the release of 5-HT [22] and, at the level of the extrapyramidal system, regulates dopamine synthesis and DA release [22–24]. Plasma levels of 5-HT 5-HIAA and Try were measured in a group of CCH patients and in a group of control subjects. The plasma levels of 5-HT and 5-HIAA resulted in the same range as those of the control group, whereas the levels of Try were significantly higher in the CCH sufferers. If these levels mirror similar changes in the CNS, this may result in the activation by Try of the inhibitory control on the serotoninergic system, PAG,

Table 1 Tyramine, octopamine, and synephrine plasma levels in control and primary headache subjects

Subjects	Tyramine	Octopamine	Synephrine
Control subjects, $n = 36$	1.05 ± 1.78	2.17 ± 1.86	3.12 ± 3.92
Migraine without aura, $n = 34$	2.02 ± 3.21	4.86 ± 2.80*	9.18 ± 4.64*
Migraine with aura, $n = 16$	1.42 ± 1.78	6.07 ± 7.10	6.77 ± 6.20
CH patients, $n = 44$	7.51 ± 7.76*†‡	11.48 ± 8.40*†	15.17 ± 12.45*§
CH patients in remission phase, $n = 20$	4.91 ± 4.36	9.86 ± 6.74*§	12.56 ± 10.90†
CH patients in active phase, $n = 24$	9.67 ± 9.67*†‡	12.84 ± 9.50*†	17.34 ± 13.43*§

Values are expressed as nanograms per milliliter ± SD and were assessed by one-way analysis of variance followed by post hoc analysis (Tamhane's test)

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CH cluster headache

*$p < 0.001$, vs controls

† $p < 0.05$, vs migraine with aura

‡ $p < 0.005$, vs migraine without aura

§ $p < 0.05$, vs migraine with aura

$p < 0.02$, vs migraine without aura

$p < 0.01$, vs controls

and related centers. This effect may explain why the duration of CH attack is shorter than that of migraine and tension-type headache in which the plasma level of this amine is significantly lower than in controls [25].

Arginine metabolism and α_1 agonists

It has been reported that the vasodilatation and pain, that accompany CH attacks, may be due to sudden release of NO in the cerebrovascular circulation [26, 27], the origin of which is unknown. We hypothesized that an increase in the synthesis and release of NO may be due to an anomalous metabolic and functional scenario involving activation of the $TAAR_1$ receptors, situated on the endothelium of the vascular system [28]. This may result in high levels of their agonists, tyramine and tryptamine, together with high levels of α_1 agonists, NE and adrenalin (E), the end result of which is an activation of endothelial NOS, release of NO, and intense vasodilatation [28]. In order to verify this, we assessed the plasma levels of Try, Tyr, NE, and E, together with the products of arginine metabolism such as arginine, homoarginine, citrulline, N^G, N^G-asymmetric dimethyl-L-arginine (ADMA), and N^G-monomethyl-L-arginine (NMMA), all products related to the synthesis and release of NO in the circulation [29], in a group of CCH patients and controls.

In comparison with control subjects, the plasma levels of tyramine, tryptamine, NE, and E were found several times higher in the plasma of CCH patients (Table 4). On the other hand, the plasma levels of arginine, homoarginine, and citrulline were significantly lower. No differences were found in the plasma levels of 5-HT, 5-HIAA, ADMA, and NMMA between CCH patients and control subjects [30] (Table 4). The results suggest that the activation of endothelial $TAAR_1$ may cause release of NO in the circulation, intense vasodilatation, and pain (Table 5).

Discussion

Different studies support the hypothesis that a complex metabolic disorder involving amino acids such as tyrosine and tryptophan plays a role in the pathogenesis of episodic and chronic CH. In episodic CH patients, plasma levels of tyramine, other elusive amines, and dopamine are significantly elevated in both the remission and active periods. One possibility is that this may reflect a biochemical shift of tyrosine metabolism involving, on one hand, an increase in the activity of the Tyr decarboxylase enzyme that transforms Tyra into Tyr and L-DOPA into dopamine and, on the other, a decrease in the activity of Tyr hydroxylase that results in a decrease in the synthesis of NE, as observed in platelets and cerebral spinal fluid of CH sufferers [31, 32]. In addition, the observation that NE levels are low in all phases of episodic CH suggests that this alteration may reflect an ongoing sympathetic dysfunction since Tyr hydroxylase is present in this system [32]. A second possibility is that the abnormal levels of elusive amines reflect hypothalamic abnormalities in the pathogenesis of CH and CCH. This is supported by several evidences: (i) the hypothalamus and locus coeruleus contain the highest levels of elusive amines, and these areas are connected with the autonomic system [33]; (ii) voxel-based morphometry MRI analysis has shown an enlarged volume of posterior part of hypothalamus in CH patients [34]; (iii) a treatment based on stereotactic stimulation of the same enlarged area significantly reduces the number of pain attacks in intractable chronic CH patients [35]; (iv) the high levels of DA found in CH and CCH patients

Table 2 Platelet trace amine levels in cluster headache (CH) patients during remission and active phases in control subjects

Subjects	Tyramine	Octopamine	Synephrine
Control subjects, $n = 22$*	0.045 ± 0.068	0.22 ± 0.16	0.33 ± 0.25
CH patients, $n = 44$	0.38 ± 0.35†	0.70 ± 0.51†	0.81 ± 0.55†
CH patients in remission phase, $n = 20$	0.43 ± 0.42‡	0.75 ± 0.53†	0.98 ± 0.62†§
CH patients in active phase, $n = 24$	0.34 ± 0.28†	0.66 ± 0.51‡	0.64 ± 0.43‡

Values are expressed as ng/10^8 platelets ± SD and were assessed by Student's unpaired *t* test

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*19 males, 3 females

† $p < 0.0001$, vs controls

‡ $p < 0.005$, vs controls

§ $p < 0.05$, vs cluster headache in active phase

suggest an activation of the dopaminergic system. It is been reported that the abnormal 24-h prolactin secretion and the blunted response to thyrotropin-releasing hormone found in CH patients are a consequence of an increased synthesis and release of DA from the dopaminergic tuberoinfundibular system that is the main inhibiting factor of PRL release from the pituitary gland [36, 37]. The neuronal cell bodies of this system are located in the arcuate and periventricular nuclei of the hypothalamus [38].

$TAAR_1$, presynaptic trace amine receptors that modulate, in inhibitory manner, the release of NE and DA in the synaptic clefts, are expressed in the hypothalamus and other structures that govern the pain threshold. The high plasma levels of elusive amines and DA that are $TAAR_1$ agonists and the low plasma levels of NE that are α_1-receptor agonists, widely distributed in the same areas, may interfere with the synaptic function of the hypothalamus and perhaps other subcortical circuitries potentially implicated in CH [30].

The pathogenesis of CCH or the chronicity process that transforms episodic CH in CCH, as occurred in some of our patients, is unclear. It is possible to conceive that the very high levels of NE and the low circulating levels of Oct and Syn, that constitute the major biochemical differences between episodic and chronic CH, may play a role in CCH. The very high levels of NE in CCH patients may derive from the loss of the inhibitory presynaptic function of $TAAR_1$ receptors. It is possible that the very great levels of Tyr, if present also in the CNS, may hyperpolarize these receptors determining a pouring of NE and DA in the competent neuronal synaptic clefts. The pathological consequences of the abnormalities in NE and DA levels may be an over-activity of the autonomic and dopaminergic systems that determine a persistent stimulation of the hypothalamus causing a continuous trigeminal activation characteristic of the active phase of CH [39].

The high levels of 5-HT and 5-HIAA in episodic cluster and the high levels of tryptamine in CCH patients suggest that the serotoninergic system is also activated as the indoles [40] and tryptamine are direct and indirect agonists of 5-HT_{1A} and 5-HT_{2A}. These receptors, located in the serotoninergic cortical system, modulate the pain sensations coming from the subcortical nuclei of the pain matrix determining the brief duration of the CH attacks. In migraine and tension-type headache patients in which the pain crisis has a much longer duration, the plasma and platelet levels of indoles and tryptamine are significantly lower than those of control subjects and CH patients [16].

Most intriguing clinical aspects of CH, as in other trigeminal autonomic headaches, are the sudden onset, very intense pain, and abrupt disappearance of the symptomatology. We hypothesized that this reflects a particular metabolic scenario that favors a high release of NO in the circulation, followed by

Table 3 Plasma levels of catecholamines and elusive amines of control subjects and cluster headache patients

	CTRL ($n = 16$)	Cluster ($n = 23$)	*p* value*
Norepinephrine	72.29 ± 33.90	214.4 ± 110.4	0.0001
Dopamine	1.92 ± 1.06	10.89 ± 8.24	0.0009
Tyramine	2.06 ± 1.61	12.51 ± 3.83	< 0.0001
Octopamine	2.54 ± 1.82	0.21 ± 0.09	< 0.0001
Synephrine	3.47 ± 3.75	0.96 ± 0.57	0.0056

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*Results are reported as mean values ± SD. *p* value was obtained by unpaired *t* test

Table 4 Plasma levels of α_1-agonists in control and cluster subjects

	CLTR ($n = 16$)	Cluster ($n = 23$)	*p* value*
Norepinephrine	72.29 ± 33.9	214.4 ± 110.4#	< 0.0001
Epinephrine	11.65 ± 2.015	21.63 ± 13.46#	0.0162

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*Values are expressed as mean ± SD. *p* value was obtained by unpaired *t* test

Nanograms per liter

Table 5 Plasma levels and ratios of arginine metabolites in control and cluster subjects

	CLTR ($n = 12$)	Cluster ($n = 23$)	p value*
Arginine	84.82 ± 16.94	53.26 ± 17.57[#]	< 0.0001
Homoarginine	1.69 ± 0.67	1.10 ± 0.48[#]	0.0052
ADMA	0.77 ± 0.11	0.9 ± 0.24[#]	0.0896
NMMA	0.08 ± 0.01	0.08 ± 0.02[#]	0.2374
Citrulline	41.10 ± 5.71	31.13 ± 10.81[#]	0.0055
Arg/ADMA ratio	2.23 ± 1.03	1.22 ± 0.43[#]	0.0003
Cit/Arg ratio	0.49 ± 0.09	0.61 ± 0.23[#]	0.1000

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*Values are expressed as mean ± SD. p value was obtained by unpaired t test

[#] Micromoles per liter

vasodilatation and intense pain. $TAAR_1$ receptors are located not only on neurons but also on the endothelium of blood vessels. In normal conditions, these receptors modulate, in an inhibitory manner, the constitutive nitric oxide synthase (NOS) enzyme that regulates the synthesis and release of NO in the circulation [41]. We believe that in CCH patients, $TAAR_1$ may invert its function and, in doing so, activates the NOS enzyme. This particular condition occurs when the levels of Tyr and Try, both agonists of $TAAR_1$, together with those of NE and E α_1 agonists, widely distributed on the same endothelial cells, are elevated in the circulation [42, 43]. This scenario in CH patients characterized by an increase in the synthesis and release of NO is supported by the findings of reduced plasma levels of arginine, homoarginine, and citrulline that are NOS substrates, in these patients.

In conclusion, complex biochemical anomalies accompany the pathogenesis of CH and CCH. Of these, changes in circulating elusive amines and catecholamines and their functional interaction with TAAR receptors may represent characteristic biochemical traits, the consequences of which result in anomalous activation of the autonomic system and the hypothalamus both of which predisposes towards the pain crisis. In support of this, treatment of CH patients with high frequency of crises, with clonidine, an $\alpha_1$receptor antagonist, significantly reduces the number of CH attacks [44]. On the other hand, the high plasma levels of TRY found in CCH may reflect an attempt of the CNS to increase the top-down control of the central serotoninergic system on the pain matrix. One consequence of this may be the length of the cluster bouts that last minutes to a few hours, instead of days as occurs in chronic migraine and tension headaches where the plasma levels of Try are low. Finally, in CCH, it is also possible that functional changes in the endothelial $TAAR_1$ receptors resulting in NO release underlie the sudden artery dilatation of the trigeminovascular system and intense pain constituting the final pathophysiological step of the cluster headache attacks [30].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any study with human subjects performed by any of the authors.

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