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Neuroendocrine Crosstalk Between PACAP and Kynurenine Pathways in Migraine Risk Among Women With PCOS

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Abstract

This narrative review examines the developing associations between polychromositis ovary syndrome (PCOS) and migraine, paying special attention to the value of pituitary adenylate cyclase-activating polypeptide (PACAP) and kynurenine pathway dysregulations. It has been indicated that PACAP, a neuropeptide that plays the role of neurovascular-inflammation and hormone regulation, may have a role in increasing the prevalence of migraine among women with PCOS. Simultaneously, the impairments in the tryptophan utilization and especially through the kynurenine pathway have been linked, not only with metabolic deficiency but also with increased neuroinflammatory activity during PCOS, which could even contribute to migraines pathogenesis. Synthesized, existing evidence is used in this review to point out an intricate engagement of hormonal, metabolic, and neurological reasons behind the comorbidity of migraine and PCOS. The learning of these common mechanisms might guide the establishment of specific treatment approaches in this high-risk patient group.

Keywords: ***Pituitary adenylate cyclase-activating polypeptide (PACAP), kynurenine pathway, tryptophan metabolism, migraine, polycystic ovary syndrome (PCOS), neuroinflammation, CGRP, women's reproductive health, metabolic dysfunction, hormone regulation.***

1.Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic condition that occurs in between 6 and 20 % of women of reproductive age. It is defined by constellation of clinical presentation that may comprise hyperandrogenism, persistent anovulation and polycystic ovarian morphology. Diagnosis is usually performed according to Rotterdam criteria that are satisfied with at least two of the following three criteria: oligo/anovulation, clinical or biochemical signs of hyperandrogenism and polycystic ovaries visualized on ultrasound. In addition to reproductive symptoms, there exists insulin resistance, obesity, type 2 diabetes and cardiovascular disease may be linked to PCOS, thus highlighting that it is multifactorial. A more recent field of interest is neuroendocrine aspect of PCOS, particularly its role in combination with neurocentral complications such as migraine(1).

Migraine is a multifactorial disabling neurovascular condition, which is not only disproportionately caused in women (almost thrice as often as in men) but also has significant effects on them. It is usually manifested with unilateral and pulsatile headaches lasting between 4-72 hours accompanied often by nausea, vomiting, photophobia, and phonophobia. The pathogenesis of migraine is included in the peripheral as well as central nerve pathways especially the trigeminovascular system activation. Neuropeptides, including calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP) have been shown to be important in the onset and extension of migraine attacks in the processes that involve the use of vasodilation and neurogenic inflammation. It has recently been found that PCOS women are more likely to have migraines and they tend to happen because of the hormonal changes, hyperandrogenism and metabolic disorders.

Of the numerous biological processes that are capable of underpinning the comorbidity between PCOS and migraine, two pathways have gained particular focus: the PACAP signaling cascade, and what is called the tryptophan-kynurenine metabolic pathway. PACAP is a neuropeptide of the vasoactive intestinal peptide (VIP)/glucagon superfamily that occurs in two active forms namely PACAP-27 and PACAP-38 in which the latter is common in human tissues. PACAP is also vital in several physiological activities, which are neurodevelopment, modulation of pain, stress response, and regulation of reproduction. Increases of PACAP have been found during migrainous attacks and it correlates with rise of trigeminal nerve sensitivity and production of pro-inflammatory cytokines. Simultaneously, PACAP, as well, is involved in regulating granulosa cells, ovarian steroidogenesis, and oocyte maturation, and is therefore a possibly plausible connection between a healthy reproductive system and healthy nervous system.

Regarding PCOS, PACAP disturbances could play a role in the abnormalities in the reproductive system in addition to the augmented migraine occurrence in women with PCOS. The hormonal environment that is typical of PCOS, namely increased luteinizing hormone (LH), resistance to insulin and elevated androgen levels, may influence the expressions of PACAP, as well as its downstream signaling. It was also observed that PACAP activity is involved in regulation of the activity of kisspeptin neurons, which determine the release of gonadotropin-releasing hormone (GnRH) and therefore LH and follicle-stimulating hormone (FSH). Such relations also confirm the idea that PACAP serves as a link between the reproductive system and neurological ones(2).

The second significant pathway in the shared pathophysiology of the migraine and PCOS is the tryptophan-kynurenine pathway. Tryptophan is a vital amino acid and a precursor of a number of bioactive compounds that includes serotonin, melatonin and kynurenines. Whereas a slight proportion of tryptophan is processed into serotonin, most of the tryptophan decompose into kynurenine route. The pathway produces a variety of neuroactive and immuno-modulatory metabolites, including kynurenic acid, quinolinic acid and xanthurenic acid. Such metabolites have the power to regulate the activity levels of the N-methyl-D-aspartate (NMDA) receptor, as well as the activity level of oxidative stress and inflammatory response which have also been shown to contribute towards the development of migraines.

Recent research has also concluded that PCOS patients exhibit profound changes in their tryptophan metabolism due to elevated serum concentrations of kynurenine and its metabolites. These metabolic imbalances frequently go together with systemic inflammation, insulin resistance, and increased C-reactive protein levels, which are the characteristics of PCOS. In addition, the kynurenine pathway dysregulation has been described in neuropsychiatric disorders, like depression and anxiety, also common in PCOS population and comorbid with chronic migraine. This potential of kynurenine metabolic products to penetrate the blood-brain barrier, influence central neurotransmission, potentially creates a mechanistic connection between metabolic disorders in the periphery and neurological consequences on the central nervous system.

This further complicates interaction between the kynurenine and PACAP pathways. Experimental data report that the antagonist of NMDA receptors, kynurenic acid is a potential mediator of the expression of the gene that codes PACAP and its protective response on pro-inflammatory activity. The possibility of neuroimmune/neuroendocrine integrated regulation in common pathophysiology of migraine and PCOS is highlighted by this interdependency. In addition, maladaptive tryptophan metabolism could exert positive effects on melatonin production, which can help to disrupt the circadian rhythm, reduce fertility, and induce susceptibility to migraine. The neuromodulatory and antioxidant functions of melatonin also enter into the emerging clinical interest, as they found that low levels of melatonin were recorded in migraineurs as well as women with PCOS(3).

Collectively, the high rates of migraine among women with PCOS seem to be of multifactorial nature including: hormonal imbalances, neuroinflammation processes, metabolic disorders and the disturbance of neuropeptide signaling. Two of those key intersections are PACAP and the kynurenine pathway, which can be viewed as possible mechanistic explanations of why this comorbidity occurs. The mechanism of the intermingled pathways is an important enlightenment to the etiology of migraine in PCOS and a new direction in the field of individual and specific treatment. For as research just begins to unfold the molecular basis behind these conditions, clinicians and researchers both must take on a multidisciplinary approach in which neurology, endocrinology, and immunometabolism play a critical role to ensure the best possible outcomes when treating this special population.

2.Methods

The aim of the present narrative review was to investigate the relationship between pituitary adenylate cyclase-activating polypeptide (PACAP) and the kynurenine pathway and the physiology of migraine in women diagnosed with polycystic ovary syndrome (PCOS). A themed approach was taken to give a synthesis and interpretation of existing literature in the fields of neuroendocrinology, metabolism, and neurology to explain their conditions of comorbidity under the same pathophysiology.

The focal aim of the research was to investigate the mechanistic and clinical data that help prove the relationship between PACAP derangement and kynurenine metabolic pathway changes and relate to the increased occurrence and dysfunction of migraines in PCOS women. The following three sub-questions informed this inquiry as follows; (1) How is PACAP involved in the generation of migraines, as well as the dysfunction of the ovaries observed in PCOS? How, then, is imbalance in the tryptophan-kynurenine pathway related to neuroinflammation and

endocrine imbalance in such patients? (3) What should be the potential implications of such an intersection on biomarker identification and therapeutic targeting?

This was done through a literature search that was established in three major electronic databases, PubMed, Embase, and Cochrane library with coverage running between January 1995 and April 2024. The search plan covered the use of Medical Subject Headings (MeSH) and free-texted keywords. Boolean operators were used to combine terms with the aim of sensitivity enhancement; these terms included terms such as, PACAP, polycystic ovary syndrome, migraine, kynurenine pathway, tryptophan metabolism, CGRP, and neuroinflammation. Other articles were found by hand searching the reference lists of important studies and reviews(4).

TABLE 1 Summary of Methodological Framework

Component	Description
Study Design	Narrative literature review
Primary Aim	To explore PACAP and kynurenine pathway involvement in migraine among women with PCOS
Databases Searched	PubMed, Embase, Cochrane Library
Search Period	January 1995 – April 2024
Search Keywords	PACAP, migraine, PCOS, kynurenine pathway, tryptophan metabolism, CGRP, neuroinflammation
Inclusion Criteria	English-language peer-reviewed articles; clinical, animal, review, and meta-analytic studies
Exclusion Criteria	Non-English studies, pediatric-focused studies, abdominal migraine only
Number of Studies Included	60 articles
Data Extracted	Study design, population, biomarkers (PACAP, kynurenine, LH), outcomes (migraine, hormonal markers)
Analysis Approach	Thematic narrative synthesis based on biological, clinical, and molecular insights
Subthemes Analyzed	PACAP's role in migraine and PCOS, kynurenine pathway in PCOS/migraine, shared pathophysiological links

Selections of the studies were made in accordance with well-defined inclusion and exclusion criteria. Studies included were published articles in English; original research (clinical and preclinical), cross-sectional and longitudinal observational studies, systemic reviews and meta-analyses, which were peer-reviewed. Research needed to directly examine one or more of the following: the implication of PACAP in PCOS or migraine; the changes in kynurenine metabolism in PCOS or migraine; or presence of both conditions and related mechanism in neuroendocrine or inflammatory implication. Studies that were not published in English, pediatric and those studies whose sole purpose is describing more about abdominal migraine without application to endocrine or metabolic pathways were not considered.

Sixty articles that fulfilled these conditions were used in the final synthesis. Two reviewers independently extracted the data to make it more objective. Data extracted were the type of study, its population, the biomarkers or hormones tested or measured (example: PACAP-38, kynurenic acid, LH, CGRP), outcome measure (example migraine frequency, hormone levels, inflammatory markers) as well as conclusions to the research questions. The dissention of the interpretation of data was settled using agreement discussion.

Because of different designs of the studies and results being measured, a narrative synthesis has been used instead of the statistical meta-analysis. The results were classified into three topics (1) PACAP role in migraine and ovarian control, (2) kynurenine pathway imbalance in PCOS and its neuroendocrine implication, and (3) shared molecular and endocrine contributors to the PCOS-migraine relationship. This framework allowed a composite overview of neuropeptide, metabolic intermediates and hormonal interactions converging and playing roles toward expression/development of the diseases(5).

Lastly, we were particularly careful with the aspect of translational relevance by suggesting possible targets of diagnosis (e.g., kynurenine/ tryptophan ratio, PACAP-38 plasma levels) and treatment (e.g., PACAP receptor

antagonists, tryptophan-metabolism modulators) that could be used in future to treat such women with PCOS and migraine.

3.Results

The literature reviewed shows a strong case on the two-way relationship between pituitary adenylate cyclase-activating polypeptide (PACAP) signaling, dysregulation of the kynurenine pathway, and comorbidity of migraine and polycystic ovary syndrome (PCOS). Sixty studies were examined and they showed the same trends in terms of molecular, endocrine, and clinical domains.

3.1 High Migraine Prevalence in PCOS Demographics

An epidemiological case indicates that women affected by PCOS are at a very high risk of migraine than general women. Among the over 19, 000 women included in a Danish cohort study, the prevalence of migraine was significantly high irrespective of obesity and other metabolic conditions among women with PCOS. This pattern was also confirmed in a number of cross-sectional and prospective studies which recorded significant elevated frequency and severity of migraines in PCOS patients. This comorbidity seems to be the most evident in women who have simultaneous hormonal changes, insulin resistance, or constant inflammation which are characteristics of the PCOS pathophysiology.

TABLE 1 Summary of Key Findings on PACAP and Kynurenine Pathway

Theme	Findings	Implications
Migraine Prevalence in PCOS	Higher migraine incidence observed in PCOS populations, independent of BMI or metabolic syndrome	Suggests a distinct neuroendocrine link in PCOS contributing to migraine susceptibility
PACAP and Migraine	Elevated PACAP-38 during migraine attacks; levels fluctuate with menstrual cycle and increase in PCOS	PACAP may act as a neuromodulator linking reproductive hormones to migraine pathophysiology
PACAP and Reproductive Function	PACAP regulates follicle development, LH/FSH secretion, and GnRH release; dysregulated in PCOS	Supports PACAP's dual role in ovarian dysfunction and neuroinflammatory states
CGRP vs. PACAP	PACAP functions independently of CGRP but has overlapping roles in vasodilation and trigeminal activation	Both contribute to migraines; PACAP may represent an additional or alternative treatment target
Kynurenine Pathway in PCOS	Increased tryptophan catabolism toward kynurenine, kynurenic acid, and quinolinic acid; linked with insulin resistance and inflammation	Highlights kynurenine pathway as a metabolic-immune axis influencing migraine and endocrine balance
Kynurenine Pathway in Migraine	Altered kynurenine metabolism observed in chronic migraine patients, especially during ictal phases	Suggests disruption in neuroprotective mechanisms involving NMDA modulation and glutamate signaling

3.2 PACAP: A Commoned Neuro-reproductive Mediator

PACAP was always found out as a major neuropeptide which affected reproductive and neurological processes. Its expression is found to be upregulated in the hypothalamus and trigeminal ganglion particularly when there is an attack of migraine. Higher plasma concentration of PACAP-38 was found to exist in migraine patients especially in women during attacks as compared to the interictal state. Notably, these were also found to be variable in terms of menstrual cycles as well as present higher in women who had PCOS(6).

PACAP is involved in physiology of ovary, promoting the survival of granulosa cell, maturity of follicle and gonadotropin release hormone (GnRH). It synergizes with the luteinizing hormone (LH), and the follicle-

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stimulating hormone (FSH) by promoting oocyte development as well as preventing apoptosis. In PCOS women, alterations of PACAP signals had related effects of elevated LH secretion, disturbed ovulation, and over-activity of follicular survival. The similar mechanisms of the two disorders and the dual role of PACAP in migraine and PCOS support the existence of a strong mechanistic connection which could be the reason why the load of headache disorders is high in the group of patients with PCOS.

3.3 CGRP and PACAP: Parallel Pathways That Are Separate

Although CGRP has been known to a long time as a major migraine mediator, several studies show that PACAP has a separate pathway uninvolved with CGRP. Both peptides escalate neurogenic inflammation and vasodilation through trigeminovascular system, whereas, PACAP also regulates reproductive hormone secretion via hypothalamus-pituitary-gonadal (HPG) axis. The presence of both CGRP and PACAP in women with PCOS was revealed to be high, and the quantity of these two neurotransmitters also appears to be linked positively to hormonal indicators, including their LH and estradiol. Both of these elevations may serve to increase the likelihood of developing migraines, in an additive manner.

3.4 PCOS and Migraine Activation of the Kynurenine Pathway

A number of metabolomic and biochemical papers pointed to the abnormal tryptophan metabolism in PCOS women. More than 90 percent of the dietary tryptophan is metabolized via the kynurenine pathway whose expression was highly up-regulated in the PCOS patients. Increased plasma concentrations of kynurenine, kynurenic acid and quinolinic acid were found most of the time and this abnormal finding was highly correlated to insulin resistance, markers of inflammation (e.g. CRP) and adiposity. Interestingly, these metabolites are neuroactive, since they can influence the activity of NMDA receptors and glutamatergic neurotransmission which is also pertinent to migraine pathophysiology.

At the same time, it was noted that migraine patients also had a dysregulated kynurenine activity, particularly in the ictal stages. Indicatively, the baseline levels of kynurenic acid (which has been characterized as an NMDA receptors blocker) of chronic migraineurs were found to be low during interictal phases hence a dampened protective mechanism(7). This confirms the supposition that disruption of the kynurenine route (i.e. increased cortical excitability accompanied by central sensitization) can provoke a reduced threshold in migraine initiation.

3.5 Effect of Hormones on PACAP and Kynurenine Interactions

Several studies were found in the review to relate reproductive hormones, PACAP and kynurenine metabolism modulation, especially estradiol and LH. Investigation revealed that PACAP promoted kisspeptin and GnRH action, which resulted in an increased release of LH massively observed in PCOS. In the meantime, augmented estrogen may enhance the breakdown of tryptophan through enhanced indoleamine 2,3-dioxygenase (IDO), which is the significant enzyme of the kynurenine pathway. Such hormonal regulation of neuroinflammatory and neuropeptide communication adds more weight on the reasons why PCOS patients might be more susceptible to migraines, especially when hormones (during menstrual periods or anovulatory periods).

3.6 Kynurenic Acid and its neuroprotective Role with Therapeutic Implications

New evidence is emerging, that kynurenic acid acylcol has a protective effect of regulating over-expression of PACAP. application of kynurenic acid in experimental migraine models also interfered with PACAP gene overexpression and also blocked PACAP- provoked vasodilation. It indicates the possibility by kynurenine-based treatment in the treatment of migraines, especially in metabolically susceptible groups of women with PCOS(8). Also, in trials, PACAP receptor antagonists and monoclonal antibodies proved to decrease the frequency and intensity of migraines, which is already a considerable step towards the personalized treatment.

5.Conclusion and Future work

Reproductive, metabolic, neuroendocrine, and neurological pathways converged in women with polycystic ovary syndrome (PCOS) create a great background of why the prevalence and severity of migraine in this population are higher than in the general population. This review highlights the pivotal importance of two closely related biological networks of interaction: of PACAP signaling and of kynurenine pathway in the development of this comorbidity.

The multifunctional neuropeptide, PACAP, is an important member of the overall equation because it plays the dual role of modulating not only the pathogenesis of migraine but also ovarian functions. The presence of elevated levels of PACAP in PCOS patients can promote the trigeminovascular activation and neurogenic inflammation, thereby increasing the vulnerability to migraines. At the same time, PACAP has an effect on reproductive hormone

release, especially on interactions with GnRH and kisspeptin neurons, which has a role in endocrine abnormalities of PCOS.

In parallel to PACAP dysregulation, there seems to be a significant alteration to the kynurenine pathway, which coordinates the tryptophan catabolism into neuroactive metabolites, in the PCOS women. Systemic inflammation, insulin resistance and neurological hyperexcitability are linked to increased concentration of kynurenine and downstream products including kynurenic and quinolinic acid. These products regulate the activity of glutamate and NMDA receptors, which connects the process of dysmetabolic regulation with migraine pathophysiology.

The mutual action of PACAP expression and activity of kynurenine pathways serves as another confirmation of the fact that the two systems cannot work independently. The hormonal changes that are prevalent with PCOS particularly those of estrogen and LH seem to modulate the release of PACAP as well as the catabolism of tryptophan. This neuroimmune-hormonal axis causes a permissive condition in migraine set up, up-regulates pain thresholds as well as enhances inflammatory reactions.

Collectively these lines of evidence point to a multidimensional framework of migraine in PCOS, which consists of hormonal dysregulation, metabolic alteration, and inflammatory effects via neuropeptides. Such insights outline new prospects of therapeutic intervention. Antagonism of PACAP receptors, manipulation of kynurenine pathway enzymes and the treatment of systemic inflammation can therefore be useful interventions against migraine in PCOS patients. Longitudinal and interventional studies to test these mechanisms and improve individually tailored treatment regimes should be the basis of research in the future.

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Conflicts of interest

The authors have no conflicts of interest to declare

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