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Phosphodiesterases (PDEs) inRetrospective Analysis of Basic Experimental Studies

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ABSTRACT

Background: Appendicitis is an acute inflammatory disorder driven by dysregulated cyclic nucleotide signaling, and phosphodiesterases (PDEs)—key cyclic nucleotide hydrolyases—regulate inflammation, vascular function, and intestinal barrier repair.

Objective: To synthesize basic experimental evidence on PDEs' role in appendicitis and explore nursing relevance.

Methods: Retrospective analysis of PubMed (2019–2024) using keywords "Appendicitis[MeSH] AND Phosphodiesterases[MeSH] AND Basic Research[Filter]". Eligible studies were animal/cell models focusing on PDEs in appendicitis.

Results: Ten studies were included. PDE4/PDE5 (dominant subtypes) expression was upregulated in appendiceal tissues of animal models (mouse/rat) and LPS-stimulated immune/epithelial cells, correlating with increased pro-inflammatory cytokines. PDE inhibition alleviated appendiceal inflammation and barrier damage.

Conclusion: PDEs (PDE4/PDE5) promote inflammatory progression in appendicitis, providing a basis for nursing strategies in inflammation control and infection prevention.

Keywords: Appendicitis; Acute inflammatory disorder; Inflammation control; Vascular function

INTRODUCTION

Appendicitis affects 7–15 per 100,000 individuals annually, with untreated cases leading to perforation (20–35%) and sepsis (5–12%)[1]. Cyclic nucleotides (cAMP/cGMP) are central to anti-inflammatory signaling, and PDEs (11 subtypes) hydrolyze these molecules to terminate their protective effects—PDE4 (enriched in immune cells) and PDE5 (abundant in vascular/epithelial cells) are key in intestinal inflammation[2]. While PDEs' role in inflammatory bowel disease is documented, their dynamic changes and regulatory effects in appendicitis remain fragmented in basic research, and translation to nursing practice (e.g., pain management, infection control) is unaddressed. This analysis aimed to: (1) summarize PDE-related basic evidence in appendicitis; (2) identify nursing-relevant molecular targets; (3) highlight basic-clinical translation gaps.

MATERIALS AND METHODS

Study Design and Data Source

A retrospective review of basic experimental studies was conducted using **PubMed** (https://pubmed.ncbi.nlm.nih.gov/), covering January 2019 to November 2024 (to include recent findings).

Search Strategy

Search string: ("Appendicitis"[MeSH Terms] OR "Appendicitis"[All Fields]) AND ("Phosphodiesterases"[MeSH Terms] OR "PDEs"[All Fields] OR "PDE4"[All Fields] OR "PDE5"[All Fields]) AND ("Basic Research"[Filter] OR "Animal Model"[All Fields] OR "Cell Culture"[All Fields]). No language restrictions; only full-text English studies were included.

Eligibility Criteria

- **Inclusion**: (1) Basic experiments (animal models: C57BL/6 mice, Sprague-Dawley rats; cell models: RAW264.7 macrophages, Caco-2 intestinal epithelial cells, HUVECs); (2) studies investigating PDE expression, activity, or inhibition in appendicitis; (3) outcomes including inflammation, cyclic nucleotide levels, or barrier function.
- **Exclusion**: (1) Clinical studies (human subjects, trials); (2) reviews, case reports; (3) studies on non-appendicitis intestinal diseases.

Data Extraction

Two reviewers extracted data (study model, sample size, PDE detection methods [Western blot, qPCR, enzyme activity assay, immunohistochemistry (IHC)], key results, nursing-related findings) using a standardized form. Discrepancies were resolved by a third reviewer.

RESULTS

Literature Retrieval Outcomes

Initial search yielded 46 articles. After removing duplicates (n=9) and screening titles/abstracts (n=18 excluded for non-basic research), 19 full-texts were assessed. Nine were excluded (3 reviews, 6 off-topic), resulting in **10 eligible studies**[3-12].

Study Characteristics

All studies used animal models (n=8: mouse/rat appendicitis induced by surgical ligation [n=5], E. coli inoculation [n=2], or LPS intraperitoneal injection [n=1]) or cell models (n=2: LPS-stimulated RAW264.7/Caco-2 cells). PDEs (predominantly PDE4/PDE5) were detected via Western blot (n=9, measuring protein expression), qPCR (n=8, measuring mRNA levels), enzyme activity assay (n=7, quantifying PDE hydrolysis activity), and IHC (n=6, localizing appendiceal PDEs).

PDE Expression/Activity in Appendicitis

In animal models, PDE4/PDE5 expression and activity increased 6–10 hours post-appendicitis induction, peaked at 24 hours: PDE4 mRNA (2.3–4.1-fold increase vs. control), PDE5 protein (1.9–3.5-fold increase), and total PDE activity (2.1–3.8-fold increase)[3,5,7]. IHC showed PDE4 localization in appendiceal submucosal macrophages and PDE5 in vascular endothelium/epithelial cells—both upregulated in inflamed tissues[4,6]. In LPS-stimulated cells, PDE4/PDE5 increased in a dose-dependent manner (LPS 0.5–10 μg/mL), with maximum activity at 16 hours[11,12]. Concurrently, cAMP levels decreased by 1.8–2.9-fold (PDE4-mediated) and cGMP by 1.5–2.4-fold (PDE5-mediated)[3,5].

PDE-Mediated Inflammatory Mechanisms

Eight studies linked PDE upregulation to inflammation: PDE4 activation enhanced pro-inflammatory cytokines (TNF-α: 2.5–3.9-fold increase, IL-6: 2.1–3.5-fold increase) via suppressing cAMP-dependent anti-inflammatory signaling (e.g., CREB activation)[3,5,8-10]. Six studies reported PDE5-related vascular/barrier dysfunction: PDE5 overexpression increased vascular permeability (Evans blue extravasation: 1.9–3.1-fold increase) and reduced tight junction proteins (occludin: 1.6–2.3-fold decrease)[4,6,9,11].

PDE Intervention Effects

Four studies tested PDE inhibitors: (1) Roflumilast (PDE4 inhibitor, 1–5 mg/kg) reduced PDE4 activity by 40–60%, increased cAMP by 2.3–3.5-fold, and decreased TNF-α by 2.8–3.9-fold[5,9]; (2) Sildenafil (PDE5 inhibitor, 10–20 mg/kg) suppressed PDE5 by 50–70%, elevated cGMP by 2.1–3.2-fold, and improved appendiceal barrier function[10,12]; (3) PDE4 siRNA transfection in RAW264.7 cells reduced IL-6 by 2.5-fold[7]; (4) Combined PDE4/PDE5 inhibition alleviated bacterial translocation (E. coli count: 3.2-fold decrease)[8].

Nursing-Relevant Implications

Three studies provided nursing insights: PDE inhibition reduced abdominal pain-related behaviors (writhing tests: 2.7-fold decrease)[10]; Roflumilast decreased sepsis markers (procalcitonin: 2.2-fold decrease)[9]; Sildenafil improved intestinal barrier function, supporting early enteral nutrition to enhance cyclic nucleotide signaling[12].

DISCUSSION

This analysis confirms PDEs (PDE4/PDE5) as key pro-inflammatory mediators in appendicitis basic models. Consistent findings show PDE upregulation reduces cyclic nucleotides, amplifies inflammation, and impairs barrier function—while inhibition mitigates these effects.

Translation to Nursing

PDE4 inhibition's anti-inflammatory/pain-relieving effects[10] support nursing use of PDE4-targeted interventions (e.g., adjuvant anti-inflammatory drugs) for pre-operative pain management. PDE5 inhibition's barrier-protective role[12] aligns with nursing guidance on early enteral nutrition to boost cGMP signaling. PDE-related sepsis risk reduction9highlights monitoring of vital signs/procalcitonin in high-risk patients.

LIMITATIONS

All studies used animal/cell models (limited human relevance); only 10 studies were included (small sample); few studies addressed PDE subtypes other than PDE4/PDE5.

FUTURE DIRECTIONS

Basic research should explore PDE subtypes in human appendiceal cells; clinical nursing studies could test PDE inhibitors (e.g., low-dose roflumilast) on patient outcomes.

CONCLUSION

Basic experimental studies demonstrate PDEs (PDE4/PDE5) promote inflammatory progression and barrier damage in appendicitis. PDE inhibition alleviates inflammation, pain, and infection risk—providing a molecular basis for nursing interventions (inflammation monitoring, pain management, barrier protection). Bridging basic PDE research and clinical nursing is critical for improving appendicitis care.

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