JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثامن والأربعون
٢٠٢٦م /١٤٤٨هـ
العدد الثامن والأربعون
(721) (693)

العلاقة البيوكيميائية بين البروينكيفالين والأمراض المزمنة

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المستخلص:

يُعدّ البروينكيفالين مؤشرًا حيويًا حديثًا حظي باهتمام كبير في السنوات الأخيرة نظرًا لأهميته المحتملة في تقييم وظائف الأعضاء والتنبؤ بمسار وتطور العديد من الأمراض المزمنة. هذا الببتيد هو طليعة الإنكيفاليات، وهي مشتقات أفيونية داخلية المنشأ تلعب دورًا حاسمًا في تنظيم عدد من العمليات الفيزيولوجية الأساسية، بما في ذلك الإحساس بالألم، وتنظيم الاستجابات الالتهابية، والحفاظ على التوازن العصبي الهرموني في الجسم. تهدف هذه المراجعة إلى تسليط الضوء على أحدث النتائج العلمية المتعلقة باستخدام البروينكيفالين كمؤشر حيوي في سياق مختلف الأمراض المزمنة، مع التركيز بشكل خاص على علاقته بوظائف الكلى، وأمراض القلب والأوعية الدموية، والاضطرابات الأيضية. تشير الأدلة الحديثة إلى أن قياس مستويات البروينكيفالين في الدم قد يوفر مؤشرًا مبكرًا ودقيقًا لاختلال وظائف الكلى، حتى في المراحل المبكرة التي قد لا تظهر فيها تغييرات واضحة في المؤشرات التقليدية. أظهرت سلسلة من الدراسات أن ارتفاع مستويات هذا المؤشر يرتبط بزيادة خطر حدوث مضاعفات في حالات أمراض الكلى المزمنة وفشل القلب، مما يعزز إمكانية استخدامه كأداة

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تنبؤيه لتقييم شدة المرض والتنبؤ بالنتائج السريرية. علاوة على ذلك، تتناول هذه المراجعة الآليات البيولوجية المحتملة التي تربط البروينكيفالين بعمليات الالتهاب والإجهاد التأكسدي والخلل الأيضي، وهي آليات محورية في تطور العديد من الأمراض المزمنة. في ضوء ذلك، يمكن اعتبار البروينكيفالين مؤشراً حيوياً واعداً ومتعدد الاستخدامات؛ ومع ذلك، لا يزال تطبيقه السريري يتطلب المزيد من الدراسات واسعة النطاق لتأكيد دقته، وتحديد نطاقاته المرجعية، واستكشاف إمكانية دمجه مع المؤشرات التشخيصية الأخرى لتحسين جودة التشخيص والتنبؤ بالنتائج السريرية.

الكلمات المفتاحية: بروينكفالين؛ الأمراض المزمنة؛ المؤشرات الحيوية؛ قصور القلب؛ مستقبلات الأفيون، داء السكري.

The biochemical relationship between proenkephalin and chronic diseases (review)

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ABSTRACT

Proenkephalin is a modern biomarker that has garnered significant attention in recent years due to its potential importance in assessing organ function and predicting the course and progression of many chronic diseases. This peptide is a precursor to enkephalins, which are endogenous opioid derivatives that play a crucial role in regulating a number of fundamental physiological processes, including pain perception, the regulation of inflammatory responses, and the maintenance of neurohormonal balance within the body.

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This review aims to highlight the latest scientific findings regarding the use of proenkephalin as a biomarker in the context of various chronic diseases, with a particular focus on its relationship to kidney function, cardiovascular diseases, and metabolic disorders. Recent evidence suggests that measuring proenkephalin levels in the blood may provide an early and accurate indicator of impaired kidney function, even in the early stages when no clear changes may be apparent in traditional markers.

A series of studies has also shown that elevated levels of this marker are associated with an increased risk of complications in cases of chronic kidney disease and heart failure, reinforcing its potential as a predictive tool for assessing disease severity and forecasting clinical outcomes. Furthermore, this review discusses the potential biological mechanisms linking proenkephalin to processes of inflammation, oxidative stress, and metabolic dysfunction—mechanisms central to the development of many chronic diseases.

In light of this, proenkephalin can be considered a promising and versatile biomarker; however, its clinical application still requires further large-scale studies to confirm its accuracy, establish its reference ranges, and explore the potential for integrating it with other diagnostic markers to improve diagnostic quality and predict clinical outcomes.

Key words: Proenkephalin; Chronic Diseases; Biomarkers; Heart Failure; Opoid Receptors, Diabetes

INTRODUCTION

Proenkephalin (penKid) is a modern biomarker that has garnered increasing attention in medical research for its potential to assess renal function and predict the course of various chronic and acute conditions. This peptide has a molecular weight of approximately 5 kilodaltons and is derived from the same molecular precursor that produces enkephalin peptides, including methionine-enkephalin and leucine-enkephalin, making it part of the body's endogenous opioid system (Walczak-Wieteska et al., 2024).

Biologically, proenkephalin is produced via the PENK gene, which encodes a precursor peptide known as preproenkephalin A, consisting of 267 amino acids, which subsequently undergoes enzymatic cleavage to produce smaller

peptides within the enkephalin family (García-Domínguez, 2024; Martin et al., 2025). These peptides include met-enkephalin and leu-enkephalin, which share a common tetra-peptide structure with a difference in the terminal amino acid (Ślusarz, 2022). Enkephalins bind specifically to delta-type opioid receptors, which are primarily concentrated in the central nervous system and are also notably present in the kidneys. Although the functional role of these peptides in the kidney remains incompletely understood, evidence suggests they may help regulate renal excretory processes such as sodium excretion and urine volume (Lin et al., 2023; Martin et al., 2025). The importance of proenkephalin lies in its greater stability compared to enkephalins, as it has a relatively long half-life of up to 48 hours, and it is not bound to plasma proteins, making it more suitable for clinical use compared to the rapidly degrading parent peptides, which have a half-life of no more than 15 minutes (Lin et al., 2023; Walczak-Wieteska et al., 2024). Proenkephalin is also freely filtered through the glomeruli without reabsorption or tubular secretion, making it a direct indicator of glomerular filtration function. Studies have demonstrated a strong inverse correlation between its plasma levels and glomerular filtration rate (GFR), supporting its use as a precise biomarker of kidney function rather than an indicator of tissue damage (B. M. & Terdal, 2024; Rau et al., 2024).
In the clinical setting, this marker has been tested in a wide range of conditions, including sepsis, acute heart failure, major surgery, severe burns, critical illness, kidney transplantation, and discontinuation of renal replacement therapy, as well as in pediatric populations (Martin et al., 2025). The results indicate that elevated levels are associated with impaired renal function and an increased risk of clinical complications. Furthermore, proenkephalin is associated with multiple physiological systems, including the nervous system, pain response, stress regulation, immune function, and neuroendocrine systems, in addition to its effects on the gastrointestinal tract, heart, and bone tissue, reflecting its potential role as a multisystem marker rather than merely a renal marker (Kanagala et al., 2019). Recent studies have also demonstrated its association with a number of chronic disorders and critical conditions, particularly heart failure with

preserved ejection fraction (HFpEF), where it serves as a predictive marker for mortality and rehospitalization (Kanagala et al., 2019). However, further complementary studies are still needed to confirm its clinical accuracy and more precisely define its diagnostic thresholds (García-Domínguez, 2024).

SITES OF PROENKEPHALIN SYNITHESIS

Proenkephalin (PENK) is widely distributed throughout many tissues, reflecting its vital role in neural, hormonal, and immune signaling networks. This peptide is primarily produced in the central nervous system, particularly in the brain, hypothalamus, and spinal cord, where it is involved in neural signal transmission and the regulation of pain and stress responses (Matsiras et al., 2025). It is also notably expressed in endocrine tissues, particularly in the adrenal medulla, suggesting its involvement in neurohormonal regulation and the response to physiological stress. Proenkephalin synthesis is not limited to the nervous system but extends to several peripheral tissues, including the heart, kidneys, gastrointestinal tract, and skin. In the heart, cardiomyocytes express proenkephalin, and its presence has been linked to the regulation of certain cardiac functions and blood circulation (Matsiras et al., 2025). In the kidneys, its production has been detected within the renal tubules and certain epithelial cells, supporting its close association with glomerular filtration function and renal homeostasis (Liu et al., 2023).

Studies have also shown that the skin is tissue rich in components of the endogenous opioid system, as keratinocytes and melanocytes contain multiple opioid receptors, in addition to their ability to produce proenkephalin, particularly after exposure to environmental stimuli such as ultraviolet radiation (Huang, 2025). A link has also been observed between proenkephalin and certain immune cells, including T cells and monocytes, suggesting its potential role in regulating the immune and inflammatory response (Assis et al., 2021).In general, the widespread distribution of proenkephalin in neural and peripheral tissues reflects its multifunctional nature and supports its role as a key component in the regulation of physiological processes associated with pain, stress, and cardiac and renal

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functions, in addition to its potential role in many chronic pathological conditions(Liu et al., 2023; Matsiras et al., 2025).

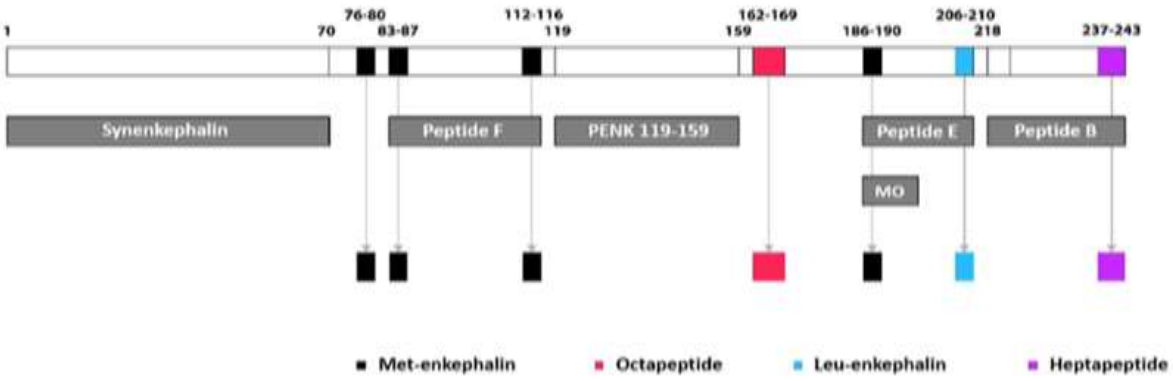

Figure 1. Human proenkephalin (Matsiras et al., 2025, Figure)

The figure illustrates the structural composition of human proenkephalin A, a precursor protein from which a group of endogenous opioid peptides of great physiological importance are derived. Proenkephalin A consists of a long amino acid chain containing several biologically active peptide segments, which are subsequently released through enzymatic proteolysis to form active peptides such as met-enkephalin and leu-enkephalin, as well as other associated peptides. The figure shows the distribution of these peptides along the proenkephalin chain, with the numbers at the top indicating the amino acid positions within the chain. The coloured regions, marked with dashed lines, indicate the sites of enzymatic cleavage where the active peptides are released. Met-enkephalin is the most abundant fragment in this protein, indicating its significant biological importance in regulating neural signaling and the pain response.

The figure also includes a number of other peptides derived from proenkephalin A, such as: Peptide F, Peptide E, Peptide B, Synenkephalin, Octapeptide and Heptapeptide.

These peptides possess diverse regulatory functions within the nervous system and other body systems. The figure also highlights the segment known as PENK 119–159, considered one of the relatively stable segments of proenkephalin and used as a biomarker in modern clinical studies, particularly for assessing kidney function and predicting acute kidney injury and cardiovascular complications (Matsiras et al., 2025, Figure).

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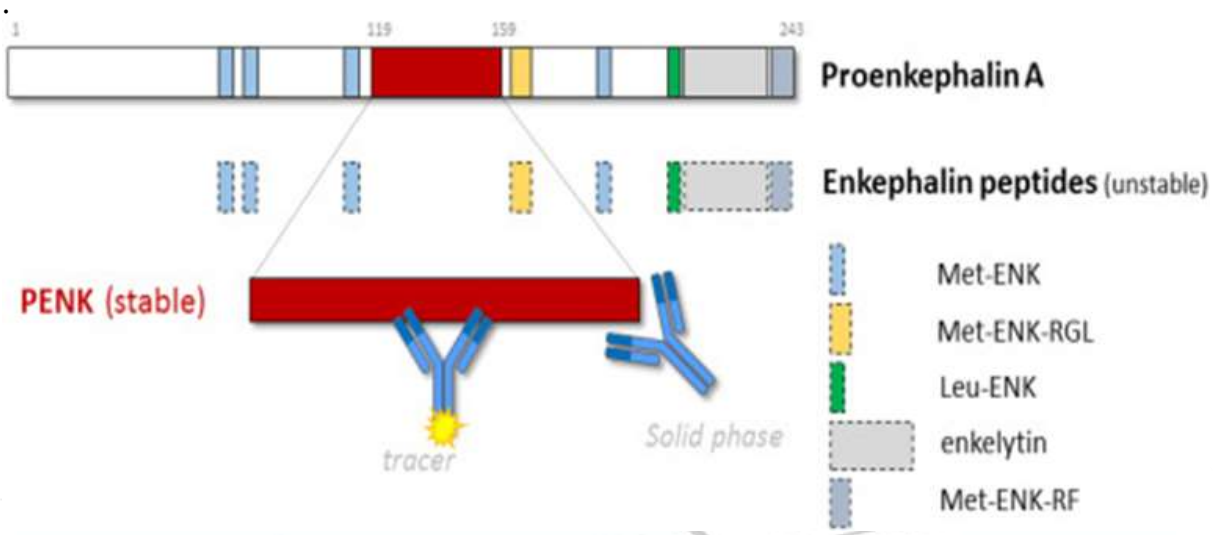

Figure 2. Proteolytic Processing of Proenkephalin 1 – 243(JACC, n.d., Figure)

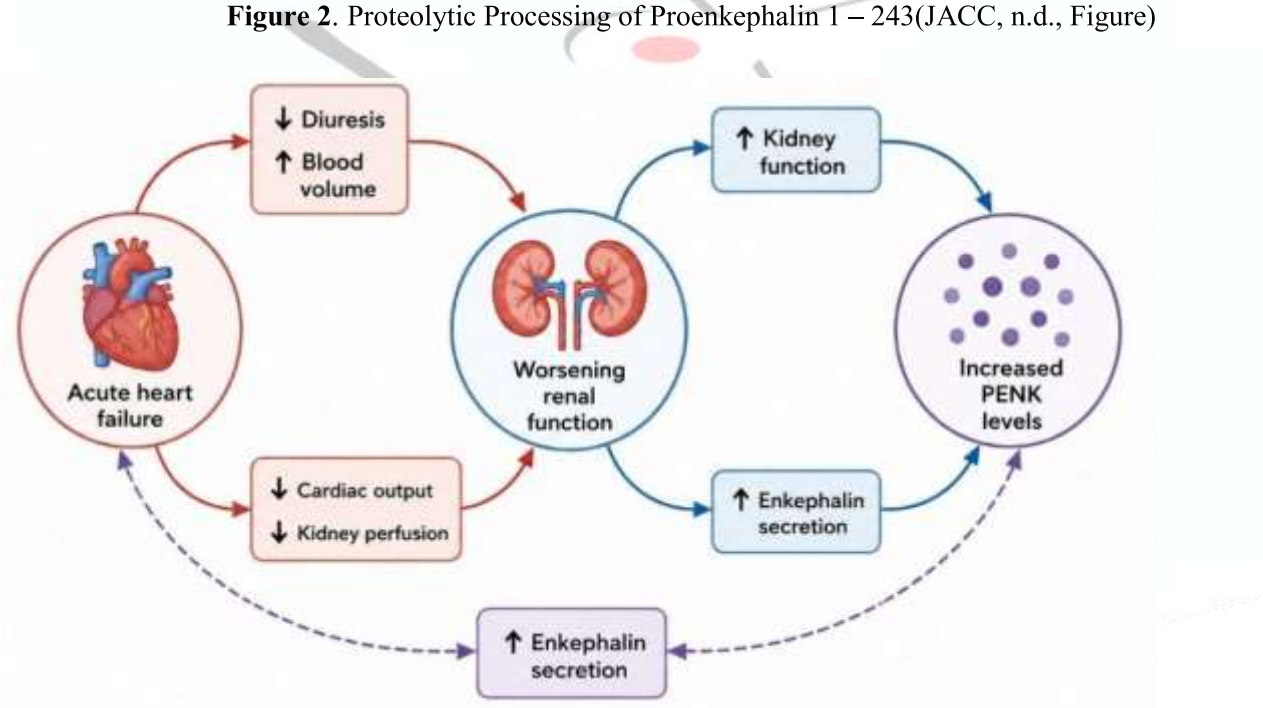

Figure 3. Proenkephalin with Heart Disorder (Adapted from Voors et al., 2017)

The figure illustrates the pathological interrelationship between acute heart failure and renal dysfunction, as well as the role of proenkephalin (PENK) as a biomarker reflecting this pathophysiological overlap. The diagram illustrates how cardiac dysfunction leads to hemodynamic disturbances that directly affect kidney function, causing elevated levels of proenkephalin in the blood.

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Initially, acute heart failure leads to a decrease in cardiac output, which reduces renal perfusion. As a result, glomerular filtration efficiency decreases, and renal function gradually deteriorates. The figure also illustrates that reduced diuresis resulting from renal insufficiency leads to an increase in blood volume and fluid within the body, which increases the volume load on the heart and exacerbates heart failure, thereby creating a vicious cycle between the heart and kidneys known as cardiorenal syndrome. The figure also indicates that the deterioration of renal function is associated with increased secretion of enkephalins, which are endogenous opioid peptides derived from proenkephalin A. Because glomerular filtration rate decreases, the kidneys' ability to eliminate these molecules declines, leading to elevated plasma concentrations of proenkephalin (PENK). Therefore, PENK is considered a sensitive and early biomarker for detecting renal dysfunction, particularly in patients with acute heart failure.

As the figure illustrates, elevated PENK levels not only reflect renal insufficiency but are also associated with the severity of heart failure and poor clinical prognosis, as studies have shown that elevated levels are linked to increased mortality rates and readmission rates in patients with heart failure. PENK is characterized by being less influenced by inflammatory factors or muscle mass compared to creatinine, making it a promising tool for the early assessment of cardio-renal dysfunction.

Overall, the figure highlights the important role of proenkephalin as a biomarker reflecting the complex interaction between the heart and kidneys, and illustrates how dysfunction in one organ can lead to dysfunction in the other through interconnected hemodynamic and neurohormonal mechanisms (Voors et al., 2017).

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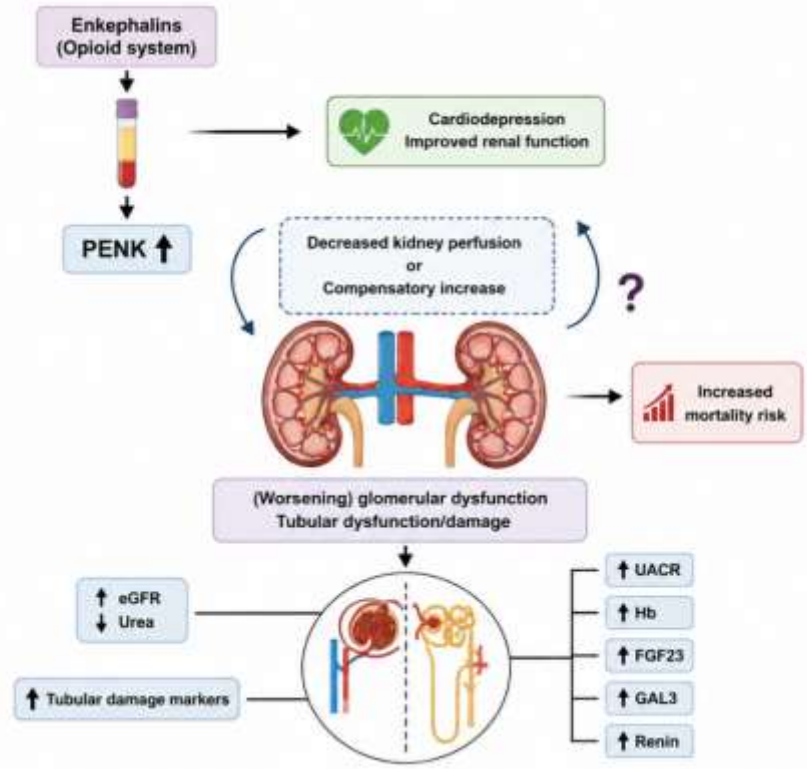

Figure 4. Effects of Proenkephalin Elevation on Renal Perfusion and Cardiac Activity (Adapted from Emmens et al., 2019)

The relationship between higher levels of PENK and (worsening) glomerular dysfunction can be explained through chronic hypoperfusion of the kidney, but the fact that higher levels of PENK respond to renal dysfunction in a counter regulatory manner is also important. The association of higher levels of PENK with tubular dysfunction/damage can be explained through chronic hypoxia, a higher degree of congestion, and oxidative stress. A plethora of biomarkers (renal) demonstrates this relationship. This could explain how PENK ends up being associated with renal dysfunction to eventually account for a significant relationship with increased risk of mortality. eGFR denotes estimated glomerular filtration rate; FGF-23 stands for fibroblast growth factor-23; GAL-3 is galectin-3; Hb stands for hemoglobin; and UACR is urine albumin-to-creatinine ratio. Servier Medical Art provided the templates (Emmens et al., 2019).

MOLECULAR REGULATION AND OPIOID RECEPTORS

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Enkephalins are endogenous opioid peptides produced in various neural and peripheral tissues, including the central and peripheral nervous systems, immune cells, and the adrenal glands, where they play an important role in regulating neural signaling and various physiological responses (Quirion et al., 2020). These peptides are formed through the enzymatic processing of the pro-enkephalin A precursor protein following transcription of the pro-enkephalin (PENK). This protein precursor undergoes a series of modifications and proteolytic cleavages that ultimately lead to the production of active opioid peptides, the most important of which are Met-enkephalin and Leu-enkephalin (Fricker et al., 2020). Other opioid peptides, such as beta-endorphin and dynorphin, may also contribute to the production of enkephalins through post-translational modifications due to their structural similarity (Conibear, 2020). The conversion of proenkephalin into active opioid peptides requires the involvement of a group of peptidase enzymes, including prohormone convertase 1 and 2, as well as carboxypeptidase E and cathepsin H, which work synergistically to produce the active form of enkephalins (Quirion et al., 2020). Once these peptides are released, their half-life is regulated by a number of degradative enzymes, such as aminopeptidase N, neprilysin, and angiotensin-converting enzyme (ACE), which help control the duration and effect of opioid signaling within tissues (Corder et al., 2018). Enkephalins primarily bind to delta-opioid receptors (δ-opioid receptors), although they can also bind to mu-opioid receptors (μ-opioid receptors); however, they exhibit a higher affinity for delta receptors (Sobocińska et al., 2019). These receptors belong to the G protein-coupled receptor (GPCR) family, which is characterized by having seven transmembrane domains and plays a central role in cellular signaling(Abrimian et al., 2021; Wang et al., 2023). When enkephalins bind to delta receptors, G-protein-coupled signaling pathways are activated, leading to the dissociation of the Gαi and Gβγ subunits and the initiation of a series of intracellular reactions (Wang et al., 2023). The Gαi subunit inhibits adenylate cyclase, thereby regulating cAMP levels and associated cellular activity, while the Gβγ subunit contributes to the opening of potassium channels and the reduction of calcium ion influx, which leads to decreased neurotransmitter release and the occurrence of inhibitory or analgesic effects (Quirion et al., 2020). Opioid receptors are widely distributed in the central and peripheral nervous systems, with a high density of delta receptors within multiple brain regions, while other regions exhibit a higher density of mu receptors (Spetea & Schmidhammer, 2020).

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Alternate splicing of opioid receptor genes also leads to the formation of multiple subtypes that differ in their functional properties and affinity for endogenous opioid peptides, in addition to differences in receptor recycling mechanisms or their transport toward intracellular degradation (Chakrabarti et al., 2021). Another important aspect is the formation of heteromer complexes between opioid receptors, such as μ-δ complexes, which exhibit different cellular signaling properties than individual receptors, as they influence G-protein coupling and opioid-related pharmacological responses. It has been suggested that this type of regulation may have therapeutic significance in reducing opioid tolerance resulting from chronic morphine use(Akgün et al., 2021; Gaborit & Massotte, 2023).
In the kidney, enkephalins and their receptors are highly expressed, particularly opioid delta receptors, as the kidney is one of the organs with the highest density of these receptors after the central nervous system. Although the precise role of enkephalins in renal tissue is not yet fully understood, current evidence suggests that they may contribute to the regulation of renal function and the dynamic balance of renal excretion (Gao & He, 2024).

PROENKEPHALIN GENE EXPRESSION

The gene expression of proenkephalin (PENK) is subject to complex regulation that depends on the interaction between neural and hormonal signals and intracellular signaling pathways; the expression levels of this peptide are influenced by a number of physiological and pathological stimuli. Studies have shown that certain neural activities, such as epileptic seizures and systemic immune challenges, can induce specific changes in proenkephalin gene expression within specific regions of the nervous system, suggesting its close association with neural adaptation mechanisms and stress response (Khorashadi et al., 2020).
Hormones also participate in the regulation of PENK gene transcription, including thyroid hormones, glucocorticoids, and estrogens, as it has been observed that estrogen stimulates increased expression of proenkephalin mRNA in a dose-dependent manner, particularly in certain brain regions associated with neuroendocrine regulation (Szentkirályi-Tóth et al., 2023). Following neural activation, a number of transcription factors are stimulated, most notably the AP-1 complex composed of FOS and JUN proteins, which binds to specific regions within the PENK gene promoter, thereby enhancing transcription and increasing proenkephalin production (Maytum et al., 2024).
Many chemical compounds interfere with the cellular pathways regulating

proenkephalin gene expression. For example, forskolin raises intracellular levels of cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA) and stimulates the transcription factors responsible for activating the PENK gene. Similarly, both retinoic acid and beta-estradiol contribute to enhancing gene transcription by binding to specific receptors that interact with response elements located within the promoter region ("Primary response gene expression," 2010). Dexamethasone and phorbol myristate acetate (PMA), on the other hand, activate glucocorticoid receptors and protein kinase C (PKC), triggering a series of intracellular signals that ultimately lead to increased proenkephalin synthesis. Furthermore, substances such as capsaicin and nicotine have been shown to enhance the gene expression of proenkephalin by activating neuronal receptors and increasing neuronal activity, reflecting the complexity of the regulatory network that controls the production of this peptide ("Primary response gene expression," 2010).

Calcium plays a pivotal role in regulating the production and release of enkephalins, as cellular depolarization leads to increased calcium ion influx and stimulates the release of enkephalins from neurons (Santa Cruz Biotechnology, n.d.). Concurrently, the synthesis of proenkephalin mRNA is stimulated to replenish depleted stores of opioid peptides (Zhu et al., 2024). Furthermore, the activation of PENK gene transcription depends on the presence of enhancers located within the 5′ end of the gene, which respond integrally to calcium and cAMP pathways, particularly via L-type calcium channels (Konradi et al., 2003; Zhu et al., 2024). It is worth noting that PENK expression is not limited to the nervous system; it has also been documented in nearby tubular epithelial cells in the kidneys, supporting its association with renal filtration functions and physiological renal regulation (Khorashadi et al., 2020; Puri et al., 2024).

INCREASED LEVELS OF PROENKEPHALIN

Proenkephalin A 119–159 (PENK) is an important modern biomarker for assessing kidney function and the early detection of acute kidney injury (AKI), as its levels rise significantly when glomerular filtration rate (GFR) decreases and kidney function is impaired (Walczak-Wieteska et al., 2025). An increase in PENK is characterized by its occurrence at earlier stages compared to serum creatinine, making it a more sensitive marker for the early detection of renal function deterioration (Arlt et al., 2026). Recent studies have shown that elevated proenkephalin levels are associated with

several pathological conditions, most notably sepsis, chronic kidney disease (CKD), and acute kidney injury, as well as in patients in intensive care units (Arlt et al., 2026; Walczak-Wieteska et al., 2025).

Its levels are also elevated in patients with heart failure due to impaired renal perfusion and reduced glomerular filtration rate associated with heart failure, and elevated concentrations have been linked to increased disease severity and higher mortality rates in these patients (Emmens et al., 2021). Furthermore, some studies have suggested a link between elevated proenkephalin and disorders of the adrenal glands and the hypothalamic-pituitary-adrenal axis, given its association with endogenous opioid peptides that are influenced by various inflammatory and hormonal conditions (Karavitaki et al., 2024). In addition, elevated PENK levels have been observed in patients with end-stage renal failure undergoing dialysis due to the severe reduction in the kidney's ability to clear it from the blood (Grycuk et al., 2023). Recent studies have confirmed that elevated proenkephalin levels can precede the onset of traditional signs of acute kidney injury by approximately 48 hours, making it highly significant for early diagnosis and reducing the development of future renal complications (Schulte et al., 2024). Therefore, proenkephalin is currently regarded as a promising biomarker associated with a number of renal, cardiac, and inflammatory conditions, with the potential for future use in early clinical assessment and monitoring of disease progression (Emmens et al., 2021; Walczak-Wieteska et al., 2025). Also, the decrease in proenkephalin level has been observed in several abnormal medical conditions, one of, these is Huntington's disease (Farag et al., 2025). It is believed that changes in this biomarker may indirectly reflect a general disruption in physiological systems associated with endogenous opioid peptides, including the enkephalin system, which plays a role in central nervous system regulation and pain and reward functions (Qiu & Wang, 2024). Some hypotheses have been proposed regarding the link between disruption of this system and neurodegenerative disorders such as Huntington's, Parkinson's, and Alzheimer's disease, as evidence suggests a dysregulation of opioid peptides within the brain due to the loss or degeneration of neurons in areas responsible for movement and memory, such as the striatum and hippocampus (Abu-Rumeileh et al., 2022). However, these changes are internal and confined to the central nervous system, and to date, there is no strong clinical evidence confirming a direct or consistent decrease in blood proenkephalin levels in these diseases, unlike what has been established in heart and kidney diseases, where PENK is used

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as a reliable biomarker with high diagnostic and predictive value (Bodnar, 2025; Shenoy & Lui, 2023). Thus, while neurodegenerative disorders may be associated with a dysfunction of the enkephalin system within the brain, direct clinical evidence of altered proenkephalin levels in the bloodstream remains limited compared to its established role in cardiac and renal diseases (Grycuk et al., 2025).

PHARMACOLOGIGAL REGULATION OF PROENKEPHALIN

Proenkephalin (PENK) levels are influenced by a number of pharmacological factors that can modulate its gene expression or bioavailability in various tissues, reflecting the potential for pharmacological regulation of this peptide system. Certain enkephalinase inhibitors, such as racecadotril (Acetorphan), are used to treat acute diarrhea, as they reduce fluid and electrolyte loss by prolonging the effects of endogenous opioid peptides, including proenkephalin derivatives (López-Campos et al., 2012). Studies also suggest that certain opioid medications, such as Tramadol, may indirectly influence proenkephalin pathways, with a potential role proposed for them in renal function recovery processes within experimental models, reflecting the overlap between the endogenous opioid system and tissue repair mechanisms (Elnagar et al., 2022). On the other hand, certain compounds that act on sigma receptors, such as SKF-10047, have demonstrated the ability to reduce proenkephalin gene expression in the brain, suggesting a role for these receptors in regulating the transcription of endogenous opioid peptides (Angulo et al., 1991). Similarly, pentazocine, a sigma receptor agonist used as a pain reliever, was found to reduce proenkephalin mRNA expression in brain regions such as the striatum and the raphe nucleus, supporting the existence of precise neural regulation of this system (Mori et al., 2015).

Overall, these findings indicate that proenkephalin expression is not static but is subject to complex pharmacological and neural regulation, opening the door to the possibility of targeting it therapeutically in various neurological, inflammatory, and renal disorders.

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PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL FUNCTIONS OF PROENKEPHALIN

Proenkephalin (PENK) is a key component of the endogenous opioid system; its enkephalin derivatives play an important role in regulating numerous neurological, immune, and hormonal processes within the body. After being processed into active opioid peptides, enkephalins bind to opioid receptors, particularly delta and mu receptors, leading to the modulation of neural signal transmission and a reduction in neurotransmitter release, thereby producing analgesic and inhibitory effects on neural activity (Cullen & Cascella, 2023; Machelska & Celik, 2020). This system also participates in regulating the response to stress and emotional arousal, in addition to its role in maintaining neurohormonal balance. Studies have shown that enkephalins contribute to the regulation of the hypothalamic-pituitary-adrenal axis, as well as their role in modulating emotional behavior and the physiological response to various stresses (Cullen & Cascella, 2023). From an immunological perspective, enkephalins exert regulatory effects on immune cells and glial cells, as they can modulate the inflammatory response, influence cytokine production, and regulate immune signaling associated with pain and neuroinflammation (Machelska & Celik, 2020). Recent evidence also points to a close overlap between the endogenous opioid system and chronic pain pathways, which has led to the development of dual enkephalinase inhibitors with the aim of prolonging the efficacy of endogenous enkephalins and improving the management of chronic pain (Southerland et al., 2021). In addition, proenkephalin is associated with a number of peripheral functions, including the regulation of cardiac and renal functions and water balance, as well as its potential role in reducing cellular damage and oxidative stress in certain pathological conditions. It is believed that these multiple effects reflect the complex nature of the endogenous opioid system and its importance in maintaining physiological homeostasis within the body (Cullen & Cascella, 2023).

ROLE OF PENK IN CARDIOVASCULAR DISEASES

Vital signs used in the assessment of heart disease, particularly heart failure, have undergone significant advancements in recent years, and their use has become an essential component of diagnosis, severity assessment, and the prediction of future complications. Although natriuretic peptides remain the most widely used biomarkers in clinical practice, proenkephalin (PENK) has

emerged as a promising biomarker closely associated with cardiac and hemodynamic disturbances (Siranart et al., 2023). Proenkephalin is a stable precursor of endogenous enkephalins, opioid peptides that exert direct effects on the cardiovascular system. These peptides interact with opioid receptors, particularly delta receptors, present in cardiac tissue, leading to a reduction in heart rate and a decrease in myocardial contractility, as well as influencing the regulation of norepinephrine release and sympathetic nerve activity (Dalefield et al., 2022). These effects are believed to contribute to the functional changes associated with heart failure and cardiac ischemia.

Recent studies have demonstrated a clear association between elevated proenkephalin levels and worsening cardiac dysfunction, including impaired ventricular filling and diastole, an increased likelihood of recurrent myocardial infarctions, as well as higher rates of hospital admissions and mortality in patients with heart failure (Banerjee et al., 2024; Siranart et al., 2023). Evidence also suggests that proenkephalin may have significant predictive value regarding disease progression and long-term clinical outcomes, which has heightened interest in it as a potential biomarker for cardiac risk assessment. Evidence also suggests that proenkephalin may have significant predictive value regarding disease progression and long-term clinical outcomes, which has heightened interest in it as a potential biomarker for cardiac risk assessment. In addition to its direct neurocardiac effects, proenkephalin may be influenced by hormonal changes associated with certain endocrine disorders, particularly thyroid disorders, which are known for their wide-ranging effects on cardiac function and circulation. Therefore, there is likely an overlap between hormonal regulation and proenkephalin levels in the context of cardiovascular diseases, reflecting the complex nature of the relationship between this biomarker and cardiac function (Soetedjo et al., 2024).

Overall, recent data suggest that proenkephalin is not merely a biomarker associated with renal function but also plays a role in predicting cardiac dysfunction and clinical outcomes in both chronic and acute heart diseases (Banerjee et al., 2024; Siranart et al., 2023).

ROLE OF PENK IN LIVER DISEASES

Recent evidence suggests that the endogenous opioid system, including proenkephalin (PENK) and its derivatives, may play an important role in regulating the balance between hepatocyte proliferation and the inflammatory response within the liver, particularly in the context of chronic

JOBS مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
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and acute liver injury. Endogenous opioid peptides are believed to contribute to the regulation of liver regeneration by influencing growth and cell proliferation signals associated with tissue repair following injury (Boyella et al., 2008).

In cases of cholestatic liver disease and biliary cirrhosis, studies have shown that the liver is not merely a target organ but may acquire the ability to locally express proenkephalin-derived peptides, suggesting the possibility that it becomes an additional source of these peptides under pathological conditions. Animal models have supported this trend, as a marked increase in proenkephalin gene expression and elevated concentrations of enkephalin peptides were observed within the liver affected by cholestatic liver disease compared to normal tissues, reflecting a close association between liver inflammation and activation of the endogenous opioid system (Bergasa et al., 1996). Recent data also suggest that this opioid regulation may extend to influence the liver's immune and viral environment, as opioid receptor-associated signaling pathways can interfere with the antiviral immune response, and may theoretically affect the replication of certain hepatic viruses and cellular response to treatment, particularly in the context of chronic inflammation and liver fibrosis (Gao & He, 2024). This opens the door to a broader understanding of the role of the endogenous opioid system as a multifunctional regulator in the pathological liver environment, rather than merely a traditional neural system. Overall, these findings suggest that proenkephalin may be part of a complex regulatory network within the liver, encompassing cell regeneration, inflammation, and the antiviral response, making it a potentially important factor in explaining the development of chronic liver diseases and their molecular mechanisms (Boyella et al., 2008; Gao & He, 2024).

ROLE OF PENK IN DIABETES MELLITUS

Type 2 diabetes is a chronic metabolic disorder characterized by persistently elevated blood glucose levels resulting from impaired insulin secretion or resistance to its action in peripheral tissues. In recent years, interest has grown in the role of the endogenous opioid system, including proenkephalin (PENK), as a potential regulator of metabolic and energy processes (Hassoun & Abass, 2025). Evidence suggests that enkephalins and their derivatives are expressed in a wide range of tissues involved in metabolic balance regulation, such as the pancreas, liver, adipose tissue, skeletal muscle, and the nervous system, reflecting their potential role in controlling

feeding behavior and glucose metabolism (Abubakar et al., 2020). In this context, it is believed that the islet cells of the pancreas may contribute to the production of proenkephalin, which may influence the regulation of glucose uptake and insulin response, suggesting a regulatory relationship between this endogenous opioid system and pancreatic metabolic function (Hassoun & Abass, 2025). On the other hand, a close association has been observed between diabetes and thyroid disorders, as rates of thyroid dysfunction are higher in diabetic patients compared to the general population, leading to reciprocal effects on insulin sensitivity and glucose metabolism (Badr et al., 2023). It has been shown that these hormonal disorders may exacerbate insulin resistance and contribute to the progression of the disease or difficulty in controlling it (Kumar et al., 2020). In this context, recent studies have shown that proenkephalin levels are significantly higher in patients with type 2 diabetes who have thyroid disorders compared to healthy or unaffected individuals, supporting its potential use as an auxiliary biomarker to distinguish between different pathological conditions. The results also suggest that proenkephalin-A may have additional diagnostic value beyond traditional markers such as HbA1c, particularly in cases where results are influenced by comorbidities such as thyroid dysfunction (Hassoun & Abass, 2025). Overall, these data suggest that proenkephalin may play a dual role—regulatory and diagnostic—in the context of diabetes, making it an important candidate as a potential biomarker in the assessment of complex metabolic disorders (Badr et al., 2023; Hassoun & Abass, 2025).

ROLE OF PENK IN KIDNEY DISEASES

Assessment of kidney function is a fundamental routine test in clinical practice within hospitals, as most patients undergo at least one kidney function assessment during their hospital stay, given the importance of early detection of any decline in renal function (Oliveira et al., 2024). Serum creatinine is widely used to estimate glomerular filtration rate (GFR); however, this marker suffers from limited accuracy due to its susceptibility to various muscular and metabolic factors, which may limit its ability to reflect early changes in renal function (Pottel et al., 2024). In addition to creatinine, blood urea nitrogen (BUN) is used as a complementary marker reflecting the kidneys' ability to eliminate protein metabolic by products; elevated levels indicate impaired glomerular filtration or reduced renal excretory function. However, this marker is also influenced by nutritional status and hydration, making it less accurate when used alone (Pottel et al.,

JOBS مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
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2024). Glomerular filtration rate (GFR) estimation equations such as CKD-EPI and MDRD are widely used in clinical assessment; however, they remain indirect estimates and may not reflect early or subtle changes in renal function, prompting the search for more sensitive and specific biomarkers (Safdar et al., 2023).

In this context, proenkephalin (PENK) has emerged as a promising biomarker for assessing renal function. It is derived from the protein precursor preproenkephalin A and is freely filtered through the glomeruli because it is not bound to plasma proteins, making it a relatively direct indicator of glomerular filtration rate (Beunders et al., 2020). Recent evidence has shown that the kidneys are the primary site for the regulation and clearance of this peptide, and that its blood levels are inversely correlated with glomerular filtration rate, reflecting its value as a sensitive marker of kidney function .Studies have also shown that elevated levels of proenkephalin are associated with impaired renal function in acute and chronic conditions, including acute kidney injury (AKI), chronic kidney disease (CKD), and critically ill patients, as well as with long-term clinical outcomes such as cardio-renal complications and increased mortality rates. Consequently, proenkephalin is considered a more stable and reliable biomarker compared to traditional markers, with the potential for use in the early and accurate assessment of kidney function (Beunders et al., 2020).

Measurement of Proenkephalin (PENK)

Proenkephalin (PENK) is commonly measured using a highly sensitive sandwich immunoassay targeting a stable fragment of the proenkephalin precursor, particularly the amino acid sequence PENK 119–159 (penKid) (Donato et al., 2018). In this method, two highly specific antibodies recognize different epitopes of the target peptide. The first antibody immobilizes the antigen on a solid phase, while the second labelled antibody binds to another epitope, forming an antibody–antigen–antibody “sandwich” complex. The generated signal is directly proportional to PENK concentration in the sample, allowing accurate quantification even at very low concentrations (Donato et al., 2018). This assay provides excellent analytical sensitivity, specificity, reproducibility, and stability, making PENK a reliable biomarker for the early detection of kidney dysfunction and acute kidney injury (Marino et al., 2015). However, despite its superior

diagnostic performance, the sandwich immunoassay is relatively expensive and requires specialized laboratory equipment and trained personnel, which may limit its routine clinical application, particularly in low-resource healthcare settings.

CONCLUSION

This study highlights the growing role of proenkephalin (PENK) as a modern multidimensional biomarker, transcending its status as a byproduct of endogenous opioid peptides to become an important regulatory and signaling component in a number of physiological and pathological systems. Recent studies suggest that PENK is closely associated with renal, cardiac, and hepatic functions, as well as metabolic disorders such as diabetes, reflecting its role as a marker that integrates multiple biological systems rather than a single organ. Data also show that PENK levels are inversely correlated with glomerular filtration rate and increase in cases of acute and chronic kidney disease, supporting its use as a more stable marker compared to traditional indicators such as creatinine. In the cardiovascular context, elevated levels are associated with an increased risk of cardiac complications and mortality, while in liver diseases and metabolic disorders, they suggest a potential role in the balance between inflammation, cellular regeneration, and hormonal response. Despite these promising findings, routine clinical use of PENK still requires large-scale prospective studies to define diagnostic thresholds, better understand its biological mechanisms, and assess its added value compared with traditional biomarkers. Accordingly, it can be considered an emerging biomarker with high potential for improving early diagnosis and clinical prognosis in a wide range of multisystem diseases.

JOBS مجلة العلوم الأساسية Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثامن والأربعون
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Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
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