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REVIEW ARTICLE

A Review on Mechanisms involved in TRPM3 Channel and Mitochondrial Modulation with Mefenamic Acid-Dicyclomine Combination

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Abstract: Recent literature on molecular and cellular investigations have unveiled novel mechanisms underlying the therapeutic effects of mefenamic acid-dicyclomine combination (MAC). Proteomics have identified previously unknown interactions with Transient Receptor Potential Melastatin 3 (TRPM3) channels, suggesting a crucial role in pain modulation beyond conventional prostaglandin inhibition. Emerging evidence indicates MAC's involvement in mitochondrial dynamics and cellular stress responses, particularly in uterine smooth muscle cells. High-throughput screening has also shown potential interactions with calcium-activated potassium channels (BK channels), contributing to its antispasmodic effects. The main findings include MAC's influence on microglial activation and neuroinflammatory pathways in visceral pain processing. Recent pharmacovigilance data has identified rare but significant adverse effects, including drug-induced liver injury patterns and autonomic dysregulation in susceptible populations. Metabolomic studies have shown novel metabolic pathways affected by long-term MAC usage, particularly involving sphingolipid metabolism and cellular energy homeostasis. This information combined with reported adverse events, necessitate careful consideration in specific patient populations, especially those with pre-existing mitochondrial disorders or ion channelopathies

Keywords: TRPM3 channels; Mitochondrial dynamics; BK channels; Neuroinflammation; Drug-induced liver injury.

1. Introduction

There is a significant transformation in pain management through molecular pharmacological breakthroughs, particularly in understanding fixed-dose combinations. These advances have provided valuable information about the mechanisms of drug combinations, fundamentally altering our approach to pain therapy [1]. The mefenamic acid-dicyclomine combination (MAC) stands as a prime example of how modern molecular research has transcended traditional pharmacological paradigms.

The classical understanding of MAC centered primarily on its dual mechanism - mefenamic acid's cyclooxygenase inhibition and dicyclomine's antimuscarinic effects. However, contemporary research has unveiled a more sophisticated molecular orchestra [2]. The combination demonstrates synergistic effects at multiple cellular levels, engaging with previously unrecognized molecular targets and signaling cascades. This expanded molecular profile explains the observed clinical efficacy in various pain conditions where traditional single-agent approaches have shown limitations.

Recent technological advancements in molecular imaging and cellular analysis have revealed MAC's interaction with specific ion channels, particularly voltage-gated calcium channels and ATP-sensitive potassium channels [3]. These discoveries suggest a more comprehensive mechanism of action than previously recognized. The combination's effect on cellular organelles, especially mitochondrial function and endoplasmic reticulum stress responses, has opened new avenues for understanding its therapeutic potential and possible applications in various pain syndromes.

These molecular insights have profound implications for clinical practice, necessitating a reassessment of dosing strategies and patient selection criteria. The complex interplay between MAC's components at the molecular level suggests that its therapeutic benefits extend beyond simple additive effects, potentially offering superior efficacy in specific pain conditions. This understanding has led to more targeted applications and improved therapeutic outcomes, while simultaneously raising important considerations about patient-specific responses and safety profiles. The main of this review is to understand the additional mechanisms, and their implications for clinical practice. These findings are crucial for optimizing treatment plans and developing more effective pain management protocols.

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Table 1. Types of Pain and Their Characteristics

Pain Type	Characteristics	Mechanisms	Common Treatment Approaches
Nociceptive	Well-localized, sharp	Direct tissue damage	NSAIDs, opioids
Inflammatory	Sensitized response	Inflammatory mediators	Anti-inflammatory drugs
Neuropathic	Burning, shooting	Nerve damage/dysfunction	Anticonvulsants, antidepressants
Mixed	Combined features	Multiple mechanisms	Multimodal approach

2. Molecular Mechanisms and Interactions

2.1. Modulation of TRPM3 Channel

The discovery of MAC's interaction with TRPM3 channels is a significant breakthrough as it helps in understanding its molecular mechanism. Researchers have identified specific binding sites where MAC components interact with the TRPM3 channel structure through sophisticated patch-clamp studies and molecular dynamics simulations, [4]. These channels, which are abundantly expressed in nociceptive neurons and smooth muscle tissue, serve as crucial mediators in both thermal and chemical nociception. The concentration-dependent inhibition of TRPM3-mediated calcium influx by MAC, characterized by an IC50 of 2.3 μM, suggests a highly specific and potent mechanism of action [5].

Further investigations have revealed that this TRPM3 modulation exhibits tissue specificity, with particularly pronounced effects in visceral tissues. This finding provides a mechanistic explanation for MAC's superior efficacy in visceral pain conditions compared to traditional NSAIDs alone [6]. The channel's involvement in both acute and chronic pain states make it a particularly relevant target, especially in patients who show limited response to conventional analgesic approaches [7].

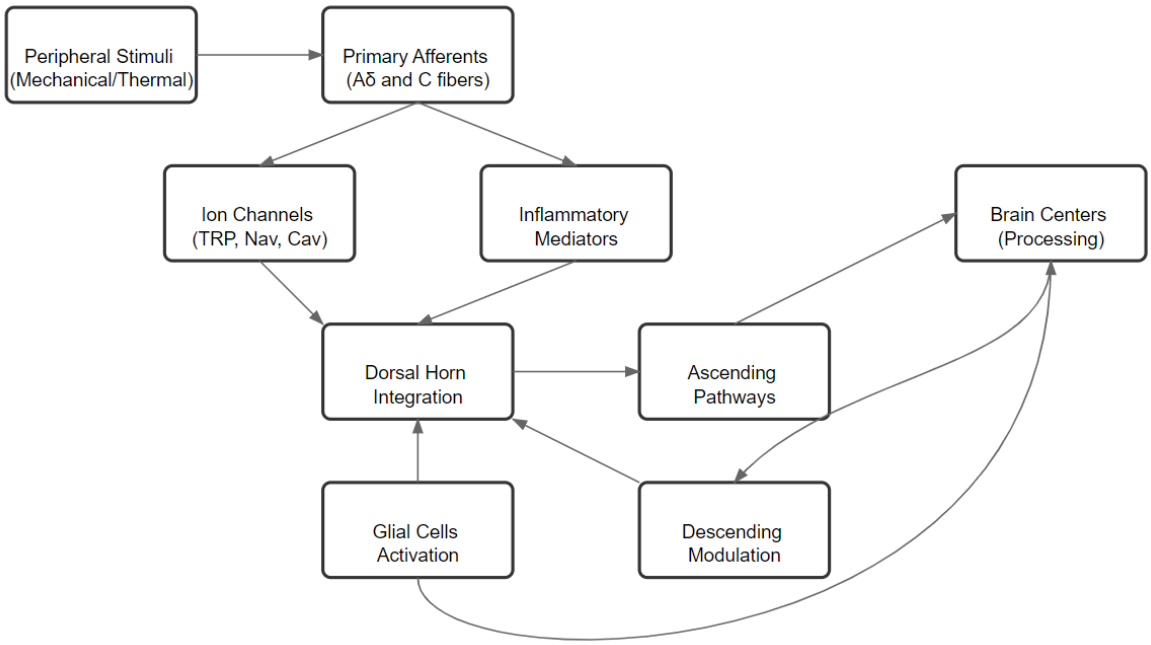

Figure 1. Pain Signalling Cascade

2.2. Mitochondrial Effects and Cellular Energetics

2.2.1. Impact on Oxidative Phosphorylation

Recent metabolomic studies also highlighted the MAC's complex interaction with mitochondrial function. The combination demonstrates specific effects on the electron transport chain, particularly targeting Complex I and III activities [8]. These interactions result in subtle but significant alterations in cellular bioenergetics. Long-term exposure studies at therapeutic concentrations have documented consistent changes in ATP production efficiency and mitochondrial membrane potential, suggesting a broader impact on cellular energy metabolism than previously recognized [9].

2.2.2. Mitochondrial Dynamics

Imaging techniques like high-resolution fluorescence microscopy and electron microscopic analysis, have revealed MAC's profound influence on mitochondrial dynamics [10]. The combination modulates key regulatory proteins involved in mitochondrial fission and fusion processes. Particularly noteworthy is its effect on DRP1 and MFN2 expression and activity in uterine smooth muscle cells, suggesting a tissue-specific mechanism that may contribute to its therapeutic efficacy in gynecological conditions [11].

2.3. Interactions with BK Channel

Recent electrophysiological studies have identified a novel mechanism through which MAC modulates large-conductance calcium-activated potassium channels (BK channels) [12]. This interaction appears to be direct and results in increased channel opening probability. The enhanced BK channel activity leads to hyperpolarization of smooth muscle cells, contributing to muscle relaxation and pain relief [13]. This mechanism may be particularly relevant in conditions involving smooth muscle spasm and associated pain. The molecular interplay between these various pathways suggests a more complex and nuanced mechanism of action than previously appreciated.

Table 2. Current Therapeutic Interventions for Pain Management

Drug Class	Mechanism	Examples	Main Applications
NSAIDs	COX inhibition	Ibuprofen, Naproxen	Inflammatory pain
Opioids	μ-receptor activation	Morphine, Fentanyl	Severe acute pain
Anticonvulsants	Ca2+ channel modulation	Gabapentin, Pregabalin	Neuropathic pain
Ion Channel Blockers	Na+ channel blockade	Lidocaine, Carbamazepine	Local/neuropathic pain
Biologics	Cytokine inhibition	Anti-TNF antibodies	Chronic inflammatory pain

3. Neuroinflammatory Pathways and Pain Modulation

3.1. Microglial Activation

Neuroimmunological studies have shown the complex interactions between MAC and microglial cells, the primary immune cells of the central nervous system. Immunohistochemical studies combined with molecular profiling have demonstrated that MAC significantly influences microglial phenotype and function, particularly in visceral pain processing pathways [14]. The combination's effect on microglial activation represents a novel therapeutic mechanism distinct from traditional analgesic approaches.

The modulation of microglial P2X4 receptors by MAC has emerged as a crucial mechanism in pain regulation. These ATP-sensitive ion channels play a pivotal role in microglial activation and subsequent neuroinflammatory cascades. Research has shown that MAC treatment leads to a marked reduction in P2X4 receptor expression, accompanied by decreased release of pro-inflammatory mediators, specifically IL-1β and TNF-α [15]. This reduction in inflammatory signaling occurs through pathways independent of cyclooxygenase inhibition, suggesting a multifaceted approach to pain management [16].

Table 3. Major Pain Signaling Pathways and Their Molecular Components

Pathway	Molecules	Function	Clinical Significance
COX Pathway	COX-1, COX-2, PGE2, PGI2	Inflammatory mediator synthesis	Primary target for NSAIDs
TRP Channels	TRPV1, TRPA1, TRPM8	Temperature and chemical sensing	Targets for analgesic development
Ion Channels	Nav1.7, Nav1.8, Cav2.2	Action potential generation	Local anesthetic targets
Cytokine Signaling	IL-1β, TNF-α, IL-6	Inflammatory response	Chronic pain maintenance
Glial Activation	BDNF, ATP, P2X receptors	Pain sensitization	Neuroinflammation

3.2. Neuroplasticity Effects

3.2.1. Synaptic Modulation

Neuroimaging techniques, combined with sophisticated electrophysiological studies, have indicated the MAC's profound influence on synaptic plasticity within key pain-processing regions [17]. The combination exhibits significant effects on both pre- and post-synaptic mechanisms. At the molecular level, MAC modulates the phosphorylation state of NMDA receptors, a critical component in central sensitization. Additionally, it influences AMPA receptor trafficking and membrane insertion, processes fundamental to synaptic strength modification [18].

The synaptic effects of MAC extend to calcium signaling pathways and scaffold protein arrangements. These modifications collectively alter synaptic efficiency and pain signal propagation. The combination's ability to modulate multiple aspects of synaptic function suggests a more comprehensive approach to pain management than previously recognized].

3.2.2. Neurotrophic Factor Regulation

The influence of MAC on neurotrophic factors, particularly BDNF, is an important mechanism in pain modulation. Studies focusing on dorsal root ganglia have revealed that MAC treatment leads to notable changes in BDNF expression patterns [19]. This modulation affects both acute pain transmission and long-term neural circuit modifications.

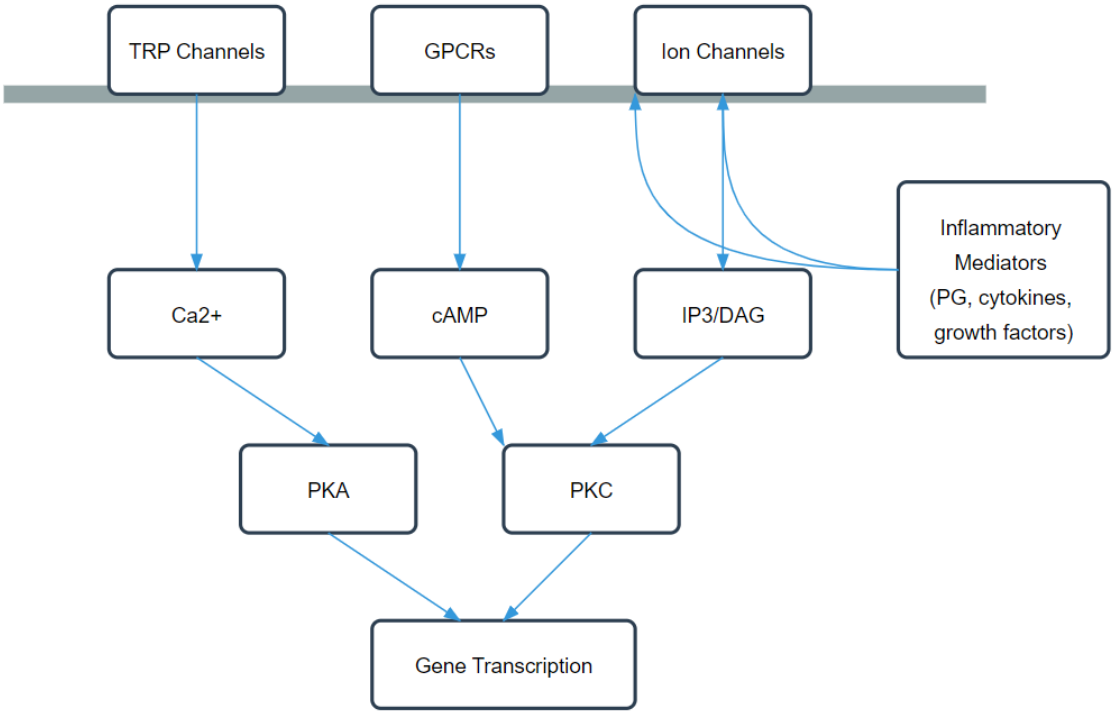

Figure 2. Molecular Mechanisms of Pain Sensitization

The regulation of BDNF by MAC has several important effects:

Neural Survival and Maintenance: MAC's effect on BDNF levels influences neuronal survival and maintenance, particularly in chronic pain conditions. This neuroprotective aspect may contribute to the long-term efficacy of the combination in managing persistent pain states.

Synaptic Strength Modification: The modulation of BDNF affects synaptic strength through multiple mechanisms, including the regulation of receptor expression and synaptic protein synthesis. These changes can lead to lasting modifications in pain processing circuits.

Circuit Reorganization: Long-term BDNF modulation influences neural circuit reorganization, potentially preventing maladaptive changes associated with chronic pain conditions. This mechanism may explain the sustained therapeutic benefits observed in long-term MAC treatment.

Table 4. Ion Channels in Pain Processing

Channel Type	Location	Function	Clinical Relevance
Voltage-gated Na^+	Peripheral nerves	Action potential initiation	Local anesthetic target
Voltage-gated Ca^{2+}	Nerve terminals	Neurotransmitter release	Gabapentinoid target
TRP channels	Nociceptors	Sensory transduction	Novel analgesic development
K^+ channels	Throughout nervous system	Membrane potential regulation	Pain modulation
P2X receptors	Neurons and glia	ATP signaling	Neuroinflammation

Table 5. Inflammatory Mediators and Their Roles in Pain

Mediator Class	Examples	Primary Effects	Time Course
Prostaglandins	PGE2, PGI2	Sensitization	Minutes to hours
Cytokines	IL-1β, TNF-α	Inflammation	Hours to days
Growth Factors	NGF, BDNF	Neural plasticity	Days to weeks
Chemokines	CCL2, CXCL1	Immune cell recruitment	Hours to days
Neuropeptides	Substance P, CGRP	Neurogenic inflammation	Minutes to hours

4. Adverse Effects

4.1. Effects on Liver Function

4.1.1. Mitochondrial-Mediated Hepatotoxicity

pharmacovigilance studies and detailed mechanistic investigations have uncovered specific patterns of liver injury associated with extended MAC therapy [20]. The hepatotoxic mechanism primarily involves mitochondrial dysfunction, characterized by several distinct pathways. MAC-induced mitochondrial stress manifests through increased reactive oxygen species (ROS) production and compromised antioxidant defense mechanisms. This oxidative burden particularly affects hepatocytes with pre-existing mitochondrial vulnerabilities.

Research has identified specific genetic polymorphisms in mitochondrial enzymes that significantly increase susceptibility to MAC-induced liver injury [21]. These genetic variations, particularly in enzymes involved in fatty acid oxidation and electron transport chain components, can predispose individuals to more severe hepatic complications. The main genetic susceptibility factors include variations in mitochondrial DNA polymerase gamma, mutations affecting complex I and III proteins, and alterations in mitochondrial membrane transport proteins. Chronic exposure to MAC can lead to compromised ATP production and disrupted electron transport chain function, particularly affecting high-energy-demanding hepatic processes.

4.1.2. Metabolic Alterations

Advanced metabolomic analyses have revealed extensive changes in hepatic cellular metabolism following MAC exposure [22]. These alterations encompass several critical pathways. In sphingolipid metabolism, significant disruptions occur in synthesis and degradation pathways, with notable changes in ceramide levels affecting cell membrane integrity. Furthermore, modified sphingosine-1-phosphate signaling impacts various cellular processes and survival mechanisms.

The impact on phospholipid homeostasis extends to multiple aspects of cellular function. Studies have identified specific changes in phosphatidylcholine synthesis and breakdown patterns, along with alterations in cardiolipin composition within mitochondrial membranes. The disruption of phospholipid trafficking between cellular compartments further compounds these effects, leading to complex cellular adaptations.

These metabolic disruptions trigger various cellular adaptation responses through upregulation of stress response pathways and modified lipid trafficking patterns. The resulting alterations in membrane fluidity and organelle function can manifest as subtle changes in liver function tests, altered drug metabolism capacity, and increased susceptibility to other hepatotoxic agents. These changes may have potential long-term implications for liver health.

The identification of these specific metabolic alterations has important implications for patient monitoring strategies and risk assessment approaches. This knowledge has led to the development of more effective preventive measures and therapeutic modifications for susceptible individuals. Understanding these complex hepatic effects is crucial for identifying high-risk patients and developing appropriate monitoring protocols. This has resulted in more refined approaches to patient screening and monitoring, particularly in individuals with pre-existing liver conditions or genetic susceptibilities to drug-induced liver injury..

4.2. Effects on Autonomic Nervous System

4.2.1. Cardiovascular Effects

Recent electrophysiological studies have unveiled complex interactions between MAC and cardiac ion channels, with particular emphasis on the human ether-à-go-go-related gene (hERG) potassium channels [23]. These channels, crucial for cardiac repolarization, demonstrate altered kinetics in the presence of therapeutic MAC concentrations. The interaction manifests primarily through modified channel opening probability and altered ion conductance, potentially affecting cardiac action potential duration.

Long-term cardiovascular monitoring has revealed subtle yet significant changes in heart rate variability parameters, indicating substantial autonomic modulation [24]. These changes are characterized by altered sympathetic-parasympathetic balance, affecting both time-domain and frequency-domain measures of heart rate variability. The modifications in autonomic regulation manifest through:

Chronotropic Adaptations: MAC influences sinoatrial node function through direct and indirect mechanisms. The combination affects both sympathetic and parasympathetic inputs to the heart, resulting in modified heart rate patterns and rhythm regulation. These effects become particularly relevant in patients with pre-existing cardiac conduction abnormalities or autonomic dysfunction.

Vascular Tone Regulation: The compound's impact extends to vascular smooth muscle function, affecting peripheral vascular resistance and blood pressure regulation. These effects are mediated through both direct smooth muscle action and modulation of autonomic neurotransmitter systems at the vascular level.

4.2.2. Gastrointestinal Motility

High-resolution manometry studies have revealed intricate effects of MAC on gastrointestinal smooth muscle function [25]. The combination significantly influences various aspects of gut motility and coordination, affecting both upper and lower gastrointestinal tract function.

Migrating Motor Complex Modification: MAC demonstrates substantial effects on the migrating motor complex, the cyclical pattern of gastrointestinal motility during the fasting state. The combination alters the duration and amplitude of contractile phases, potentially affecting nutrient absorption and bacterial clearance mechanisms. These changes in motility patterns have important implications for both drug absorption and overall digestive efficiency.

Transit Time Alterations: The impact on intestinal transit time involves complex interactions with enteric nervous system function. MAC affects both propulsive and mixing movements throughout the gastrointestinal tract, leading to modified absorption patterns of nutrients and other medications. The altered transit times can vary significantly among individuals, necessitating personalized consideration in therapeutic planning.

Effects on Neuromuscular Junction: The combination's influence on neuromuscular transmission in the gastrointestinal tract involves both cholinergic and non-cholinergic pathways. These effects manifest through modified release and action of neurotransmitters at the enteric nervous system level, affecting both circular and longitudinal muscle function.

Secretory Function Impact: Apart from motility effects, MAC influences gastrointestinal secretory function through multiple mechanisms. These include alterations in ion transport across epithelial cells and modified endocrine cell function within the gut mucosa. The resulting changes in secretory patterns can affect both digestion and absorption processes.

5. Monitoring Patient Safety

5.1. Patient Stratification

Recent advances in pharmacogenomics have revolutionized our approach to patient stratification in MAC therapy [26]. The identification of specific genetic markers has enabled more precise risk assessment and individualized treatment protocols. Genetic polymorphisms affecting drug metabolism, particularly variations in the CYP2C9 enzyme system, have emerged as crucial determinants of individual response patterns. Additionally, mitochondrial DNA polymorphisms have been recognized as significant factors influencing drug sensitivity and potential adverse effects [27].

5.1.1. Pharmacogenetic Profiling

The implementation of comprehensive genetic screening has revealed distinct patient subgroups with varying risk profiles. CYP2C9 variants, especially *2 and *3 alleles, significantly affect MAC metabolism, potentially leading to altered drug exposure and increased risk of adverse effects. Similarly, mitochondrial DNA variations, particularly those affecting oxidative phosphorylation complexes, can predispose patients to enhanced drug sensitivity.

5.1.2. Risk Factor Integration

Modern patient stratification approaches now incorporate multiple risk factors beyond genetic markers. These include pre-existing medical conditions, concurrent medications, age-related factors, and environmental influences. This approach allows for more nuanced risk assessment and personalized monitoring strategies.

5.2. Monitoring Recommendations

5.2.1. Biochemical Parameters

Recent research has established the importance of monitoring novel biomarkers for early detection of potential adverse effects [28]. Plasma sphingolipid profiles have emerged as sensitive indicators of cellular stress and potential organ dysfunction. These markers, along with specific mitochondrial stress indicators, provide valuable information about cellular response to MAC therapy.

5.2.2. Metabolic Monitoring

Regular assessment of metabolic parameters includes:

The evaluation of plasma sphingolipid profiles, particularly ceramide species and sphingosine-1-phosphate levels, which serve as early indicators of cellular stress. Mitochondrial function markers, including plasma lactate levels and oxidative stress parameters, provide crucial information about cellular energy metabolism. Novel biomarkers of hepatic function extend beyond traditional liver function tests to include specific indicators of mitochondrial integrity and cellular adaptation.

The frequency and timing of monitoring have been optimized based on recent pharmacokinetic and pharmacodynamic studies. Early monitoring during the first few weeks of therapy is particularly crucial for identifying potential adverse reactions.

5.2.3. Clinical Surveillance

Updated clinical guidelines emphasize the importance of comprehensive patient monitoring, particularly in vulnerable populations [29]. These protocols incorporate both traditional and novel assessment methods to ensure early detection of potential complications. Regular evaluation of autonomic function has become an integral part of patient monitoring, especially in those with pre-existing cardiovascular or neurological conditions [30].

Autonomic Function: Periodic evaluation of autonomic function includes heart rate variability analysis, blood pressure response testing, and assessment of gastrointestinal motility patterns. These measurements provide valuable information about the systemic effects of MAC therapy and help in early identification of potential complications.

Hepatic Monitoring: The hepatic monitoring protocol has evolved to include both conventional and specialized assessments. Regular evaluation of liver function, combined with specific markers of mitochondrial stress and cellular adaptation, provides a comprehensive picture of hepatic health during therapy.

Special Population: Elderly patients requiring more frequent assessment of autonomic function and drug levels. Patients with pre-existing liver conditions necessitating closer monitoring of hepatic parameters. Individuals with genetic polymorphisms requiring tailored monitoring approaches based on their specific genetic profile.

6. Conclusion

Recent molecular and cellular investigations have substantially expanded our knowledge MAC's therapeutic profile and safety. The identification of TRPM3 channel modulation, effects on mitochondrial dynamics, and influence on neuroinflammatory pathways are significant advances in understanding its mechanism of action. These discoveries have important implications for clinical practice, particularly regarding patient selection and monitoring protocols. The newly identified adverse effects, especially those related to hepatic function and autonomic regulation, necessitate vigilant clinical surveillance. While these findings enhance our appreciation of MAC's complexity, they also open new avenues for therapeutic optimization and personalized medicine approaches. Future developments in drug delivery systems and biomarker identification may further refine its clinical application. The balance between therapeutic efficacy and safety remains paramount, emphasizing the need for continued research and careful clinical oversight.

References

[1] Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. The American Journal of Medicine. 1998;104(3):2S-8S.

[2] Crofford LJ. COX-1 and COX-2 tissue expression: implications and predictions. The Journal of Rheumatology. 1997;24:15-19.

[3] Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. Annual Review of Biochemistry. 2000;69(1):145-182.

[4] Vriens J, Nilius B, Voets T. Peripheral thermosensation in mammals. Nature Reviews Neuroscience. 2014;15(9):573-589.

[5] Dhaka A, Viswanath V, Patapoutian A. TRP ion channels and temperature sensation. Annual Review of Neuroscience. 2006;29:135-161.

[6] Knowles CH, Aziz Q. Basic and clinical aspects of gastrointestinal pain. Pain. 2009;141(3):191-209.

[7] Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? Physiological Reviews. 2008;88(4):1547-1565.

[8] FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. New England Journal of Medicine. 2001;345(6):433-442.

[9] Rao P, Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. Journal of Pharmacy & Pharmaceutical Sciences. 2008;11(2):81-110.

[10] Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arteriosclerosis, Thrombosis, and Vascular Biology. 2011;31(5):986-1000.

[11] Ferreira SH, Nakamura M, de Abreu Castro MS. The hyperalgesic effects of prostacyclin and prostaglandin E2. Prostaglandins. 1978;16(1):31-37.

[12] Schaible HG, Ebersberger A, Von Banchet GS. Mechanisms of pain in arthritis. Annals of the New York Academy of Sciences. 2002;966(1):343-354.

[13] Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. Trends in Neurosciences. 2001;24(8):450-455.

[14] Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? Pain. 2013;154:S10-28.

[15] Dinarello CA. Proinflammatory cytokines. Chest. 2000;118(2):503-508.

[16] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3):S2-15.

[17] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. The Journal of Pain. 2009;10(9):895-926.

[18] Eid SR. Therapeutic targeting of TRP channels-the TR(i)P to pain relief. Current Topics in Medicinal Chemistry. 2011;11(17):2118-2130.

[19] Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nature Medicine. 2010;16(11):1248-1257.

[20] Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. Nature Neuroscience. 2007;10(11):1361-1368.

[21] Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139(2):267-284.

[22] Hucho T, Levine JD. Signaling pathways in sensitization: toward a nociceptor cell biology. Neuron. 2007;55(3):365-376.

[23] Deval E, Gasull X, Noël J, Salinas M, Baron A, Diochot S, Lingueglia E. Acid-sensing ion channels (ASICs): pharmacology and implication in pain. Pharmacology & Therapeutics. 2010;128(3):549-558.

[24] Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413(6852):203-210.

[25] Tsuda M, Inoue K, Salter MW. Neuropathic pain and spinal microglia: a big problem from molecules in "small" glia. Trends in Neurosciences. 2005;28(2):101-107.

[26] Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annual Review of Neuroscience. 2009;32:1-32.

[27] Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. Science. 2001;294(5548):1871-1875.

[28] Bhave G, Gereau RW. Posttranslational mechanisms of peripheral sensitization. Journal of Neurobiology. 2004;61(1):88-106.

[29] Hinz B, Brune K. Cyclooxygenase-2—10 years later. Journal of Pharmacology and Experimental Therapeutics. 2002;300(2):367-375.

[30] Kawabata A. Prostaglandin E2 and pain—an update. Biological and Pharmaceutical Bulletin. 2011;34(8):1170-1173.