The Effect Of Bile Acid Derivatives On Smooth Muscle Function Through Calcium Ion Channels

Sodiqova Shodiyakhon Solijonovna
Lecturer, Kokand University
ORCID ID 0009-0000-6633-4140
shsodiqova@kokanduni.uz

Introduction

In recent decades, the development of pharmaceutical and biomedical sciences has increasingly focused on the in-depth study of biologically active compounds, especially those derived from natural sources. This is due to the fact that naturally sourced substances often show better compatibility with the human body, lower toxicity, and broad-spectrum pharmacological activity. From this perspective, bile acids and their derivatives occupy an important place in pharmaceutical research.

Among bile acids, ursodeoxycholic acid (UDCA) holds particular importance. As a secondary bile acid, it plays a role in dissolving cholesterol, optimizing bile composition, enhancing bile flow, and providing hepatoprotective and antioxidant effects (Beuers et al., 2018). UDCA is an approved standard treatment in many countries for dissolving cholesterol gallstones, treating primary biliary cirrhosis, hepatitis, and other liver diseases.

However, recent scientific investigations have revealed that the pharmacological properties of UDCA and its derivatives extend far beyond the liver. Notably, their direct effects on smooth muscle cells have been demonstrated, including the ability to regulate muscle tone and induce vasodilation (the widening of blood vessels). This suggests that bile acid derivatives may serve not only as hepatoprotective agents, but also as potential spasmolytic and vasoprotective drugs (Sattarov et al., 2020; Kim et al., 2018).

From the standpoint of smooth muscle physiology and pharmacology, muscle contraction is primarily regulated by the influx of calcium ions into cells. L-type calcium channels play a central role in this process. The release of calcium from the sarcoplasmic reticulum and its entry through the cell membrane triggers smooth muscle contraction. Therefore, calcium channel blockers are widely used in the treatment of conditions such as hypertension, angina pectoris, and smooth muscle spasms (Somlyo & Somlyo, 2003).

Scientific evidence regarding the influence of bile acid derivatives on these channels further expands their potential pharmacological applications. For example, in a study by Sattarov et al. (2020), bile acid derivatives significantly reduced calcium influx in smooth muscle byinhibiting L-type VDCCs. Additionally, Kim et al. (2018) found that UDCA enhances NO synthesis in endothelial cells, which in turn promotes smooth muscle relaxation.

This scientific article aims to thoroughly analyze the mechanisms by which bile acid derivatives affect smooth muscle function through calcium ion channels, assess their pharmacological significance, and synthesize the available literature. The findings may provide a theoretical and practical foundation for the development of new spasmolytic and vasoprotective drugs in the future.

Literature Review

Bile Acids and Their General Pharmacological Properties Ursodeoxycholic acid (UDCA) is a naturally occurring secondary bile acid synthesized from cholesterol in the human body. In the liver, cholesterol undergoes initial modification by the enzyme 7α-hydroxylase, followed by sequential hydroxylation and oxidation reactions to produce various bile acids. Among these, UDCA stands out due to its unique physicochemical and biological properties.

The primary pharmacological effects of UDCA include:

- Hepatoprotective effect: UDCA stabilizes hepatocyte membranes, reduces the cytotoxicity of bile acids, and mitigates oxidative stress. These properties make it widely applicable in the treatment of primary biliary cirrhosis, hepatitis, alcoholic liver disease, and drug-induced hepatopathies (Beuers et al., 2018).
- Cholesterol-dissolving action: By increasing the solubility of cholesterol in bile, UDCA helps dissolve gallstones. This effect is related to the stabilization of cholesterol in micellar solutions.
- Stimulation of bile secretion: UDCA enhances bile secretion, improving bile flow in cholestatic conditions — an effect particularly valuable in biliary dyskinesia.
- Anti-apoptotic properties: Research shows that UDCA reduces apoptosis (programmed cell death) in hepatocytes, thereby preserving cell viability (Beuers et al., 2018).

For these reasons, UDCA is currently considered a standard therapeutic agent in gastroenterology and hepatology.

Study	***Objective***	***Result***	***Conclusion***
Sattarov et al. (2020)	To investigate the effect of bile acid derivatives on calcium influx	At a concentration of 20 μM, calcium influx decreased by 38 ± 3%	Bile acid derivatives may act as L-type VDCC (voltage-dependent calcium channel) inhibitors
Kim et al. (2018)	To study the effect of bile acids on NO production in endothelial cells	NO synthesis increased by 45%	Increased NO production enhances muscle relaxation via cGMP
Park et al. (2021)	To examine the effect of bile acid and calcium channel blocker combination	The combination enhanced vasorelaxation up to 70%	Bile acids and calcium channel blockers exert a synergistic effect

From the analysis of these studies, it is evident that bile acid derivatives promote smooth muscle relaxation via two main mechanisms:

1. Direct inhibition of L-type VDCCs, i.e., by limiting the influx of calcium ions into muscle cells.
2. Stimulation of endothelial NO production, which enhances guanylate cyclase activity and increases cGMP levels, leading to muscle relaxation.

Furthermore, research by Park et al. (2021) demonstrated that the combined use of bile acid derivatives and calcium channel blockers significantly increased smooth muscle relaxation. This opens up promising perspectives for combination therapy strategies in pharmacology.

Main Body

The mechanism of action of bile acid derivatives on smooth muscle involves several complex molecular pathways. The two primary mechanisms are as follows:

Inhibition of L-type VDCCs

Smooth muscle contraction is largely dependent on the entry of calcium ions into the cell. The most critical stage in this process is the opening of L-type voltage-dependent calcium channels (VDCCs), allowing Ca^{2+} ions to flow into the cytoplasm. These channels, located on the cell membrane, contain an α1 subunit, which serves as the primary functional component of the channel.

Studies show that bile acid derivatives bind to the α1 subunit, altering the channel's conformation (Sattarov et al., 2020). As a result, the probability of the channel opening is reduced, significantly decreasing calcium influx.

This process unfolds in several steps:

- Reduced calcium influx: Under normal conditions, membrane depolarization triggers the opening of L-type VDCCs, allowing Ca^{2+} to enter the cell. Bile acid derivatives inhibit this process.

- Reduced MLCK activation: With decreased intracellular calcium levels, the calcium–calmodulin complex fails to form, which in turn prevents the activation of myosin light chain kinase (MLCK).
- Decreased myosin phosphorylation: Without MLCK activity, the light chains of myosin are not phosphorylated, limiting the interaction of myosin heads with actin filaments.
- Muscle relaxation: As a result, the muscle tone is reduced, leading to relaxation of smooth muscle.

Although this mechanism resembles the pharmacodynamics of calcium channel blockers (e.g., nifedipine, verapamil), bile acid derivatives have the added advantage of being natural substances with additional hepatoprotective and metabolic benefits.

Stimulation of Endothelial NO Production

The second key pathway by which bile acid derivatives induce smooth muscle relaxation is through the activation of endothelial nitric oxide synthase (eNOS). Within endothelial cells, eNOS synthesizes nitric oxide (NO) from L-arginine. Studies have shown that bile acid derivatives increase eNOS expression and its enzymatic activity (Kim et al., 2018).

The process follows these steps:

- Bile acid derivatives activate eNOS.
- NO production increases and diffuses from the endothelial cell to adjacent smooth muscle cells.
- NO activates guanylate cyclase, increasing cGMP levels.
- cGMP activates myosin light chain phosphatase (MLCP).
- MLCP dephosphorylates the light chains of myosin.
- Consequently, myosin heads lose their ability to bind to actin, leading to muscle relaxation.

This mechanism is similar to the pathway utilized by pharmacological NO donors (e.g., nitroglycerin, isosorbide dinitrate). However, since the action of bile acid derivatives is natural and associated with fewer side effects, they offer a promising option for long-term use.

Summary

Thus, bile acid derivatives induce smooth muscle relaxation via two primary mechanisms:

- Inhibition of calcium influx (ion channel inhibition)
- Activation of the NO–cGMP–MLCP pathway

These properties grant them spasmolytic, vasodilatory, and hypotensive effects, making them suitable for pharmacological use in conditions such as hypertension, angiospasm, biliary dyskinesia, and urological spasms.

Diagram 1: Mechanisms of Action of Bile Acid Derivatives

In modern medicine and pharmacology, the study of biologically active compounds of natural origin is one of the most urgent and relevant research areas. Among such promising compounds are bile acid derivatives, whose multifaceted pharmacological properties are increasingly attracting the attention of the scientific community. Initially considered as mere

components of bile secretions, these derivatives are now recognized for their potential therapeutic effects on multiple systems — from the cardiovascular system to liver function.

First and foremost, the role of bile acid derivatives in the treatment of hypertension deserves special attention. Research shows that these compounds directly affect the contraction of vascular smooth muscles by blocking calcium ion channels, which qualifies them as naturally derived calcium channel blockers. Their reduced side effect profile, compared to conventional pharmacological agents, enhances their clinical value and applicability.

In addition, bile acid derivatives exhibit spasmolytic effects on the biliary tract, making them effective for symptomatic relief in conditions such as cholangitis, cholelithiasis, and other bile duct-related disorders. Their broad activity on smooth muscles extends not only to blood vessels but also to the gastrointestinal and biliary systems.

The hepatoprotective properties of bile acid derivatives, such as ursodeoxycholic acid (UDCA) and taurocholic acid (TCA), also deserve independent emphasis. Due to their antioxidant and anti-inflammatory effects, these compounds have shown efficacy in conditions such as chronic hepatitis, hepatic fibrosis, and toxic liver injuries. Notably, they have been scientifically proven to inhibit apoptosis at the cellular level, stabilize mitochondrial function, and reduce reactive oxygen species (ROS) levels.

From a pharmaceutical industry perspective, bile acid derivatives are now seen as a novel molecular foundation for developing next-generation bioactive drugs. Their natural origin, multifunctional activity, and relatively low toxicity make them ideal candidates for use in combination therapies. The possibility of synergistic effects with other pharmacological agents further amplifies their clinical potential.

An intriguing aspect of recent research is the exploration of bile acid derivatives in sports medicine. Their potential use as muscle relaxants during post-exertional recovery or muscle spasms is being investigated (Park et al., 2021). This could significantly expand their therapeutic application range.

In conclusion, bile acid derivatives are among the most promising bioactive compounds in contemporary medicine. Their diverse pharmacological profile — spanning cardiovascular health, liver protection, and even sports recovery — opens wide prospects for future scientific and clinical advancements. Without a doubt, further in-depth studies in this area may mark a new era in pharmacology centered around bile acid derivatives.

Conclusion

Bile acids and their derivatives exert smooth muscle relaxation through two primary molecular pathways:

- Inhibition of calcium ion channels, and
- Nitric oxide (NO) signaling activation.

These mechanisms position them as potentially valuable pharmacological agents for the treatment of hypertension, bile duct disorders, and other conditions requiring spasmolytic therapy.

Future scientific research should aim to fully evaluate the therapeutic potential of these compounds and expand their clinical applications by focusing on the following directions:

- Structural modifications to improve bioactivity and selectivity;
- In vivo safety assessments to establish comprehensive toxicity profiles;
- In-depth pharmacokinetic studies to explore their absorption, distribution, metabolism, and excretion (ADME) characteristics.

Based on these approaches, bile acid derivatives could serve as a crucial molecular platform for pharmaceutical development and the creation of new therapeutic drugs.

References:

Beuers, U., Trauner, M., Jansen, P., & Poupon, R. (2018). New paradigms in the treatment of cholestatic liver diseases. Hepatology, 67(1), 305-312.

Kim, Y. et al. (2018). Bile acids and nitric oxide production in endothelial cells. Vascular Pharmacology, 102, 23-29.

Park, S. et al. (2021). Synergistic effects of bile acid derivatives with calcium channel blockers. Korean Journal of Physiology & Pharmacology, 25(4), 445-452.

Sattarov, M. et al. (2020). Effect of bile acid derivatives on calcium channels in smooth muscles. Journal of Pharmacological Research, 45(2), 120-127.

Somlyo, A. P., & Somlyo, A. V. (2003). Ca^{2+} sensitivity of smooth muscle and nonmuscle myosin II: modulated by G proteins, kinases, and myosin phosphatase. Physiological Reviews, 83(4), 1325-1358.