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Natriuretic Peptides and Calcium Signaling in Cardiac Myofibroblasts: Experimental Models, Ac16 Cells and Related Systems

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SUMMARY

Natriuretic peptides (primarily ANP, BNP, and CNP) are cardiac hormones with fundamental endocrine and paracrine functions in cardiovascular homeostasis. Their signaling through receptors with guanylate cyclase activity (NPR-A and NPR-B) and the NPR-C receptor regulates physiological and pathological processes, such as cGMP modulation, cell proliferation, fibrosis, and intracellular calcium homeostasis. Although most of the literature has focused on generic cardiomyocytes or cardiac fibroblasts, there is evidence indicating that These signals can indirectly modulate Ca^{2+} release and the myofibroblastic phenotypeespecially via cGMP/PKG-dependent mechanisms or L-type calcium inhibition, with potential antifibrotic impact.

Natriuretic Peptide System and Intracellular Signaling

Composition and Receptors

The PNs include:

- ANP (atrial natriuretic peptide)
- BNP (B-type natriuretic peptide)
- CNP (C-type natriuretic peptide)
- These join:
- **NPR-A/GC-A**: main ligand of ANP and BNP → ↑cGMP via guanylate cyclase.
- **NPR-B/GC-B**: preferential receptor for CNP → ↑cGMP.
- **NPR-C**: traditionally considered a "capture/degradation" receptor, but with the ability to signal via Gi that modulates cAMP and influences ion channels. Wikipedia

The generation ofc GMP triggers effects through PKG (protein kinase G), regulation of ion channels, and other cellular targets, and negatively modulates pro-fibrogenic pathways such as TGF-β1. MDPI

Calcium Signaling Mechanisms Affected by Natriuretics

Direct Effects on Calcium Channels

Although there are no direct studies on AC16 myofibroblasts, classic works show that:

- CNP using NPR-Ccan inhibit currents ofL-type Ca^{2+} channelsin cardiomyocytes, reducing Ca^{2+} influx and modulating excitability. PubMed

This modulation of the Ca^{2+} channel suggests a potential *indirect effect* in tra cellular Ca^{2+} loads also occur in non-excitable cells (such as fibroblasts), since Ca^{2+}-dependent channels can influence profibrotic signaling pathways.

cGMP-Dependent Signaling and Ca^{2+}

The increase in cGMP by ANP/BNP/CNP can have multiple effects on Ca^{2+} regulation:

- Activation ofPKG, which can modulate proteins that interact with the Ca^{2+} release and reuptake machinery.
- Interaction with Ca^{2+} channels mediating entry or mobilization, for example, TRP channels or SOCE ventilators involved in cardiac fibroblasts. PMC

Effects of Natriuretics on Cardiac Fibroblasts and Myofibroblasts

Proliferation, Differentiation and Fibrosis

Several lines of research show:

- ANP and BNP inhibit proliferation and transformation to myofibroblastsand decrease the synthesis of extracellular matrix in cardiac fibroblasts. MDPI+1
- This occurs through antagonism to profibrogenic signals (TGF-β1, AngII), modulating intracellular Ca^{2+} signaling indirectly by suppressing fibrogenesis-dependent Ca^{2+} promoting pathways. MDPI

Although these actions have not been directly linked to Ca^{2+} release in AC16 myofibroblasts, the The inhibitory role in proliferation and transformation suggests a modulation of Ca^{2+}-dependent routes, since Ion Ca^{2+} is central to the activation of differentiation pathways (e.g. IP_3, TRP, SOCE). MDPI

Ca^{2+} Signals in Cardiac Fibroblasts

Cardiac fibroblasts depend on increases in intracellular Ca^{2+} for differentiation into myofibroblasts and ECM production. Multiple channels and mechanisms—such as IP_3-R, TRP channels, SOCE, Orai1— give shape to these Ca^{2+} signals. MDPI, PNs, by modulating second messenger pathways (cGMP/PKG), can interact with these pathways by modulating the global intracellular Ca^{2+} profile, although this effect requires specific direct evidence for AC16 or human cardiac myofibroblasts.

Integration of Natriuretic Signals with Calcium Signaling in Cardiac Remodeling

Anti-Fibrosis Mechanisms

PN antagonize fibrogenic signals that typically trigger elevated Ca^{2+} responses in fibroblasts:

- Inhibition of TGF-β1and the activation of Smad mediated by PKG. PubMed
- They reduce proliferation and conversion to myofibroblasts. MDPI

Connectivity with Ca^{2+} Signals

Although many studies of Ca^{2+} in fibroblasts focus on TRP channels, SOCE, and other mechanical sensors, PN via cGMP can indirectly affect these pathways by modulating the expression or function of those proteins [1-6].

Conclusion and Knowledge Gaps

- Direct evidence of Ca^{2+} release in AC16 myofibroblasts in response to PN is limited or nonexistent.
- In general cardiac cells, PN modulate Ca^{2+} influx (e.g., inhibition of L-type channels by CNP/NPR-C). PubMed
- In cardiac fibroblasts, PN inhibit profibrogenic pathways and transformation to myofibroblast, which implies influence on Ca^{2+}-dependent signaling of profibrogens such as TGF-β1. MDPI
- Ca^{2+} pathways (IP_3, SOCE, TRP) are central to fibroblast activation, and natriuretics can modulate these pathwaysindirectlythrough effects on second messengers and pro/anti-fibrotic signals, but Specific evidence is required in AC16 or equivalent human models.

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