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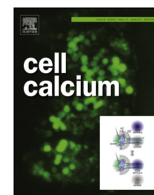

Review

Vasopressin-induced Ca^{2+} signals in human adipose-derived stem cells

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ABSTRACT

Intracellular Ca^{2+} signals are essential for stem cell differentiation due to their ability to control signaling pathways involved in this process. Arginine vasopression (AVP) is a neurohypophyseal hormone that increases intracellular Ca^{2+} concentration during adipogenesis via V1a receptors, Gq-proteins and the PLC–IP_3 pathway in human adipose-derived stromal/stem cells (hASCs). These Ca^{2+} signals originate through calcium release from pools within the endoplasmic reticulum and the extracellular space. AVP supplementation to the adipogenic media inhibits adipogenesis and key adipocyte marker genes. This review focuses on the intersection between AVP, Ca^{2+} signals and ASC differentiation.

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1. Introduction

In the United States, the total cost related to adolescent obesity alone is estimated to be $254 billion [1]. Therefore, understanding the mechanisms controlling adipogenesis by stromal/stem cells will be necessary to identify signal transduction pathways as potential targets for obesity prevention and intervention. Intracellular Ca^{2+} signaling controls many processes related to stromal/stem cell function, including fertilization, proliferation, development, differentiation, contraction, and secretion [2]. Calcium oscillations stimulate transcription factors and gene expression [3]. They are important for the G_1/S phase of the cell cycle and originate from IP_3-mediated Ca^{2+} release from the endoplasmic reticulum (ER) in embryonic stem cells (ESCs) and bone marrow-derived stromal/stem cells (BMSCs) [4,5]. In addition, they are observed during stem cell differentiation but frequently cease at the stage of terminal differentiation [6,7]. Physical manipulation of Ca^{2+} signals increases osteogenesis in hBMSCs by activating the mitogen-activated protein kinase (MAPK) pathway [8]. It also up-regulates peroxisome proliferator-activated receptor γ (PPARγ) gene expression, a master transcription factor for adipogenesis, but inhibits its expression at later stages of stromal/stem cell adipogenesis [9]. Recently, we reported that arginine vasopressin (AVP) increases intracellular Ca^{2+} concentration and inhibits adipocyte differentiation in human adipose-derived stromal/stem cells (hASCs) [10]. The overall goal of this review is to summarize the known effects of AVP on Ca^{2+} signaling during the differentiation of hASC and related stromal/stem cells.

1.1. Human adipose-derived stromal/stem cells

The origin of the majority of hASCs is from the mesodermal layer of the embryo [11]. The hASC are multipotent cells that can

Abbreviations: AVP, arginine vasopressin; hASCs, human adipose-derived stromal/stem cells; hBMSCs, human bone marrow-derived stromal/stem cells; cAMP, cyclic adenosine monophosphate; C/EBP, CCAAT/enhancer-binding protein; CFU, colony forming unit; CRAC, Ca^{2+} release-activated Ca^{2+} channels; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ESCs, embryonic stem cells; FABP4, fatty acid binding protein 4; IP_3, inositol-1,4,5-triphosphate; MAPK, mitogen-activated protein kinase; miRNA, micro-ribonucleic acid; MLR, mixed lymphocyte reaction; PI3K/Akt/mTOR, phosphoinositide-3-kinase/Akt/mammalian target of rapamycin; PIP_2, phosphatidylinositol-4,5-biphosphate; PLC, phospholipase C; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; SOCs, store-operated Ca^{2+} channels; STIM, stromal interaction molecule; SVF, stromal vascular fraction; TRPM7, transient receptor potential melastatin 7; TRPV, transient receptor potential vanilloid; VDCCs, voltage-dependent Ca^{2+} channels.

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differentiate in vitro into cells expressing biochemical characteristics unique to adipocytes, chondrocytes, osteoblasts, hepatocytes, myocytes, and pancreatic-like cells [12]. They have a fibroblastic morphology, colony-forming unit (CFU) ability, and share similar surface antigens with other MSCs such as $CD44^+$, $CD73^+$, $CD90^+$, $CD105^+$, $CD45^-$, and $CD31^-$ [13]. Unlike the freshly isolated heterogeneous population found in the stromal vascular fraction (SVF) cells of adipose tissue, the adherent, culture expanded and passaged hASC display reduced immunogenicity and fail to elicit a robust T lymphocyte activation during in vitro mixed lymphocyte reactions (MLR) [14]. In addition, hASCs can induce dendritic cell tolerance in co-cultures by inhibiting $CD4^+$ T cell activation [15]. The hASCs have a normal karyotype, reduced telomerase levels and cease proliferation after extended culture periods (up to passage 30) [16]. There is evidence that hASCs isolated from different donors vary with respect to their adipogenic capability [17]. Intracellular Ca^{2+} oscillations in undifferentiated hASCs are dependent on Ca^{2+} release and influx and may be involved in stem cell maintenance [18].

Multiple signaling pathways control adipogenesis and osteogenesis in hASCs. For example, extracellular signal-regulated kinase (ERK) suppression inhibits osteogenesis but induces adipogenesis [19,20]. Endogenous Wnt signaling inhibits osteogenesis but has no effect on adipogenesis while Notch signaling inhibits adipogenesis [21,22]. However, other reports show that Wnt signaling increases osteogenic differentiation but down-regulates adipogenic differentiation [23,24]. The Hedgehog signaling pathway controls adipocyte maturation by reducing C/EBPα and PPARγ expression and insulin sensitivity [25]. Moreover, Nell-1 signaling cross talks with the Hedgehog pathway to inhibit adipogenesis [26]. Epidermal and fibroblast growth factors increase proliferation, adipogenesis and insulin sensitivity [27]. miRNAs, such as miR-17-5p and miR-106a, inhibit osteogenesis and facilitate adipogenesis, while miR-22 has the opposite effects [28,29]. Hypoxia increases adipogenesis by stimulating the PI3K/Akt/mTOR pathway [30]. Autologous platelet-rich plasma and insulin treatment can also stimulate adipogenic differentiation via Akt [31]. In contrast, the role of Ca^{2+} signaling on the hASC differentiation process remains relatively unknown.

1.2. Calcium signaling in mesenchymal stem cells

Stem cells have ion channels within their plasma membrane that are responsible for Ca^{2+} movement into cells. Below is an overview of the different ion channels and signaling pathways known so far.

1.2.1. Voltage-dependent Ca^{2+} channels

Voltage-dependent Ca^{2+} channels (VDCCs) are expressed predominantly in excitable cells such as neurons, skeletal myocytes, and heart myocytes [32]. Due to their depolarization, open VDCCs promote Ca^{2+} influx into the cells, leading to various cellular responses such as hormone secretion, neurotransmitter release, and muscle contraction [32]. In addition, VDCCs are expressed in non-excitable cells such as hASCs and hBMSCs [33–35]. L-type VDCCs ($Ca_V1.2$) have been reported in hBMSCs [34,35], and L-type VDCCs ($Ca_V1.2$) and T-type VDCCs ($Ca_V3.2$) are present in hASCs [36]. In rat dental pulp stem cells, the $Ca_V1.2$ is needed for neural differentiation as knockdown inhibits this process [37].

1.2.2. Store-operated Ca^{2+} channels

Store-operated Ca^{2+} channels (SOCs), also known as Ca^{2+} release-activated Ca^{2+} channels (CRAC), are activated by the phospholipase C (PLC) pathway which catalyzes phosphatidylinositol-4,5-biphosphate (PIP_2) conversion to inositol-1,4,5-triphosphate (IP_3); this, in turn, binds to the ER to promote Ca^{2+} release into the cytoplasm [38]. When the ER is depleted of Ca^{2+}, stromal interaction molecule (STIM), a Ca^{2+} ER sensor, translocates to SOCs to promote Ca^{2+} influx [39]. This channel is the main Ca^{2+} entry pathway in non-excitable cells [40], is highly selective for Ca^{2+} ions, and is only permeable to monovalent cations in divalent free extracellular solution [41,42]. Mutation of two conserved negatively charged glutamate residues decreases the Ca^{2+} entry via SOCs in T lymphocytes [43]. The Orai1, Orai2, Orai3 are the main components of SOCs of which Orai1 forms the channel pore [44–46]. Orai1 is a membrane protein with four transmembrane segments with intracellular C and N termini [43,44]. Orai1 or Orai2/Orai3 overexpression with STIM1 amplifies CRAC currents; Orai1, but not Orai2 or Orai3, is inhibited by intracellular Ca^{2+} [46,47]. Orai1 and STIM1 are important for AVP-induced Ca^{2+} oscillations and entry in rat hepatocytes [48]. Furthermore, the CRAC channel is regulated by pH because acidification diminishes while alkalization facilitates its activity [49].

1.2.3. Additional ion channels

Voltage-gated K^+ channels, especially subunit Kv2.1, play an important role in adipogenesis of hBMSCs because their suppression dramatically reduces lipid droplet accumulation and fatty acid binding protein 4 (FABP4) expression [50]. The Kir6.1, Kir6.2 and SUR2A components of the ATP-sensitive K^+ channels are expressed in hBMSCs [51]. In these stem cells, Kir6.1 and SUR2A mRNA expression decreases during adipogenic differentiation while Kir6.2 mRNA is up-regulated during osteogenesis [51]. In addition, inhibition of large conductance Ca^{2+}-activated K^+ or ether-à-go-go K^+ channels reduces adipogenesis and osteogenesis in hBMSCs [52]. Knockdown of transient receptor potential vanilloid (TRPV) 2, TRPV4, or transient receptor potential melastatin 7 (TRPM7) reduce adipogenesis in human pre-adipocytes by decreasing phosphorylated Akt kinase [53].

1.2.4. The phospholipase C—Inositol triphosphate pathway

Phospholipase C (PLC) was first detected as an amylase secretion released by the pancreas after treatment with acetylcholine and carbamylcholine [54]. Later, PLC was identified as the enzyme catalyzing PIP_2 conversion to IP_3 and diacylglycerol (DAG) [55]. There are 13 PLC family members that are subdivided into 6 classes (β, γ, δ, ζ, ε, and η) [56]. Of these, PLCβ, PLCδ and PLCη are linked to Gq-coupled receptors, PLCγ and PLCζ to tyrosine-kinase receptors, and PLCε is coupled to both receptor types [56].

Inositol-1,4,5-triphosphate's (IP_3) function in calcium release was determined initially when pancreatic acinar cells were found to release ER Ca^{2+} following carbachol stimulation [57,58]. There are 3 types of IP_3 receptors (IP_3R): IP_3R1, IP_3R2 and IP_3R3 [59]. All three are major contributors to Ca^{2+} release in undifferentiated hBMSCs [34]. IP_3-induced Ca^{2+} release is crucial for Ca^{2+} oscillations in stem cells since IP_3R antagonists inhibit Ca^{2+} signals [4–6]. Human pre-adipocytes including hASCs also express all three IP_3Rs that are involved in intracellular Ca^{2+} oscillations [60,61].

1.3. Arginine vasopressin

AVP, a nine amino acid peptide is involved in several physiological/pathological functions such as behavior, thermoregulation and water reabsorption [62]. AVP exerts its effect by binding to three types of receptors: V1a, V1b and V2. These receptors are G-protein-coupled with seven transmembrane domains [63].

2. Effect of AVP on Ca^{2+} signals in stromal/stem cells

As hASCs are a suitable model for adipogenic studies, we investigated the role of AVP on hASC differentiation [13]. We found V1a receptor gene expression in hASCs and AVP inhibits adipogenesis in this stem cell type [10]. This is consistent with murine V1a receptor mutation or knockout strains that display a

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