# Chapter 14
# Mechanosensitivity of Pancreatic β-cells, Adipocytes, and Skeletal Muscle Cells: The Therapeutic Targets of Metabolic Syndrome

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## 14.1 Introduction

Mechanotransduction describes the molecular and cellular processes that transduce mechanical/physical forces, such as hemodynamic factors, exercise, and osmotic change, into biochemical signals, followed by diverse intracellular signaling and cell responses, thus enabling organisms from bacteria to human beings to adapt to their physical surroundings (Jaalouk and Lammerding 2009). As mechanosensing and its feedback system are fundamental for physiological homeostasis, failures in mechanotransduction would cause various pathological conditions.

The cardiovascular system is known to be particularly sensitive to mechanical stimuli such as cardiac contraction, blood pressure, and blood flow. We have recently reviewed specific mechanotransduction signaling involved in myogenic responses of cerebral arteries (Nakayama et al. 2010): Spatial and temporal interactions of mechanosensitive kinases including Rho/Rho-kinase, protein kinase C, and tyrosine kinase were discussed. These kinases are also activated in experimental canine cerebral vasospasm after subarachnoid hemorrhage, and play an important role in the development of the vasospasm. Thus, the mechanism underlying stretch-induced contraction and cerebral vasospastic episode may overlap.

The metabolic syndrome is characterized by a group of metabolic risk factors, including diabetic diseases, abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and prothrombotic and proinflammatory states in one person (Scott et al. 2004). Progression of the metabolic syndrome leads to increased risk of coronary heart disease and other vascular occlusive diseases related to plaque buildup in arterial walls. It is a well-documented fact that non-sensory cells and tissues

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derived from mesenchyme, including stromal cells like cardiac, smooth, and skeletal muscles, endothelial cells, fibroblasts, and osteoblasts are mechanosensitive. Adipocytes are also derived from mesenchyme, while pancreatic β-cells are derived from endodermal epithelium. Interestingly, these latter two types of cells are also mechanosensitive. Thus it is worth extending the research field of mechanotransduction into pancreatic β-cells, adipocytes, and skeletal muscle cells, all of which are related to the core concerns in metabolic syndrome.

Pancreatic β-cells are inflated by a high glucose level, which leads to insulin secretion independently of the well-documented $K_{ATP}$ channel-dependent mechanism. Adipocytes subjected to mechanical stretching show a variety of phenotype and functional changes. Moreover, passive stretching in skeletal muscle cells promotes surface expression of glucose transporter 4 (GLUT4) and facilitates glucose uptake. Thus it seems possible that the level of blood glucose may be controlled via mechanosensitive mechanisms, which may open the way to a new therapeutic strategy of diabetic diseases.

The present article focuses on the unitary discussion of three peripheral organs from the view point of mechanosensitivity/mechanotransduction. We provide herein some new insights into the mechanotransduction of pancreatic β-cells, adipocytes, and skeletal muscle cells, based on our series of published papers and those of others in related fields, i.e., how the cell/tissue is sensing mechanical force, and transducing it into intracellular signaling and other events related to energy metabolism.

## 14.2 Pancreatic β-Cell

### *14.2.1 Introduction*

Glucose-stimulated insulin secretion (GSIS) from pancreatic β-cells is attributed to a sequence of events; acceleration of metabolism, closure of ATP-sensitive $K^+$ ($K_{ATP}$) channels, membrane depolarization, activation of voltage-dependent $Ca^{2+}$ channels (VDCC), and a rise in cytosolic free $Ca^{2+}$ concentration ($[Ca^{2+}]_c$) through $Ca^{2+}$ influx (Ashcroft and Rorsman 1990; Newsholme et al. 2010). A major aspect of GSIS is, therefore, the induction of electrical activity. The membrane potential of β-cells at sub-stimulatory glucose concentrations is normally between −60 and −70 mV and the cells are electrically silent. The elevation of glucose concentration results in a gradually developing depolarization, and action potentials are generated when the membrane potential reaches the threshold potential. This $K_{ATP}$ channel-dependent triggering signal is essential for GSIS. The $K_{ATP}$ channels of β-cells are a heteromultimer composed of the pore-forming Kir6.2 and the sulfonylurea receptor SUR1 (Drews et al. 2010). However, GSIS is unlikely to be exclusively dependent only on the $K_{ATP}$ channel-dependent mechanism. GSIS consists of two phases; a transient and marked first phase, followed by a sustained flat or gradually increasing second phase. The possible mechanisms underlying the two phases of GSIS have been previously reviewed (Straub and Sharp 2002; Henquin 2009). The first phase

is currently ascribed to a rapid, $K_{ATP}$ channel–dependent increase in $[Ca^{2+}]_c$ that triggers exocytosis of a readily releasable pool of insulin granules. The second phase requires both the triggering $[Ca^{2+}]_c$ elevation and the augmentation of exocytosis via a $K_{ATP}$ channel–independent mechanism. The latter pathway has been estimated under the conditions where the involvement of $K_{ATP}$ channels is eliminated by either $K_{ATP}$ channel openers or blockers (Komatsu et al. 2001). Although the second phase has been suggested to be caused by various possible mechanisms, the molecular mechanism still remains to be established.

Functional $K_{ATP}$ channels are well known to be essential for β-cell activity. However, the ionic mechanism triggering insulin secretion, especially in the second phase, is still a matter of debate. Evidence has been accumulating that inhibition of $K_{ATP}$ channels is not the sole ionic mechanism underlying the depolarization in response to glucose elevation in β-cells. For example, low concentrations of glucose decreased $^{42}K^+$ or $^{86}Rb^+$ efflux from pancreatic islets, probably reflecting $K_{ATP}$ channel inhibition; however, the $K^+$ conductance was little affected or rather transiently increased when the concentration of glucose exceeded approximately 8.3 mM (Henquin 1978; Carpinelli and Malaisse 1981). Moreover, $K_{ATP}$ channels were shown to be inhibited by glucose within the range 0–5 mM with no further effect of higher concentrations (Ashcroft et al. 1988; Best 2002a). Consistent with these findings, the membrane conductance of β-cells was the minimum at threshold concentrations of glucose but rather increased at stimulatory glucose concentrations (Best 2000). Moreover, glucose depolarized the membrane potential even in the β-cells where $K_{ATP}$ channels were completely inhibited by sulfonylurea $K_{ATP}$ channel blockers (Best 2002a) and in the β-cells from Kir6.2 knock-out mice (Ravier et al. 2009). In the β-cells from SUR1 knock-out mice, although they displayed action potentials even at low glucose concentrations, changes in action potential frequency, percentage of time with action potentials, and interburst length were still observed when glucose concentration was raised (Düfer et al. 2004). It is thus highly possible that ionic mechanisms other than $K_{ATP}$ channel inhibition are involved in the membrane depolarization induced by higher concentrations of glucose in β-cells. In particular, the alternative ionic mechanisms may be of importance in pathophysiological conditions, as in type 2 diabetes mellitus, where insulin secretion during hyperglycemia cannot be satisfactorily explained by the closure of $K_{ATP}$ channels. The responses to β-cell swelling have been postulated as one of the candidate mechanisms.

### *14.2.2 β-Cell Swelling Induced by High-Concentration Glucose*

Of particular interest is the fact that glucose causes the swelling of β-cells (Semino et al. 1990; Miley et al. 1997; Takii et al. 2006). Glucose-induced β-cell swelling is dependent on glucose metabolism, because it is not evoked by 3-*O*-methylglucose, a non-metabolizable glucose analogue (Miley et al. 1997; Davies et al. 2007). The mechanisms can be explained as follows: The elevation of glucose concentration accelerates glycolysis, leading to an accumulation of lactate, a product of non-oxidative

phosphorylation. The expression of the plasma membrane monocarboxylate transporter MCT1, which transports lactate as well as pyruvate, is unusually low in β-cells (Best et al. 1992; Zhao et al. 2001). This modification would serve a role to prevent the loss of glucose-derived pyruvate from β-cells; on the other hand, it would lead to intracellular lactate accumulation when the cells are exposed to high concentrations of glucose. Indeed, there is evidence that an accumulation of lactate formed from methylglyoxal leads to β-cell swelling (Best et al. 1999). The intracellular accumulation of lactate would result in intracellular hyperosmolarity, producing cell swelling (Best et al. 1992; Sekine et al. 1994). A controversial point, however, exists regarding the capacity of β-cells to generate lactate during glucose stimulation. As well as MCT1, lactate dehydrogenase (LDH), which converts pyruvate to lactate, displays very low expression levels in β-cells (Sekine et al. 1994), suggesting that LDH activity in β-cells may not be sufficient to convert pyruvate generated from glucose to lactate. As an alternative mechanism for glucose-induced β-cell swelling, an involvement of $Na^+/H^+$ and $Cl^-/HCO_3^-$ exchangers is proposed. These exchangers are of importance in the extrusion of $H^+$ and $HCO_3^-$ generated by glucose metabolism (Grapengiesser et al. 1989; Shepherd and Henquin 1995). Their activation increases the intracellular concentrations of $Na^+$ and $Cl^-$, leading to intracellular hyperosmolarity (Best et al. 1997). Since osmotic β-cell swelling induces insulin secretion (Blackard et al. 1975; Best et al. 1996a; Drews et al. 1998), the swelling due to high-concentration glucose is expected to be one of the mechanisms underlying GSIS.

### *14.2.3 Volume-Regulated Anion Channels*

Volume-regulated anion channels (VRAC) are ubiquitously expressed in mammalian cells and are known to play a pivotal role in the cell volume regulation system, regulatory volume decrease (RVD), which occurs after hypotonicity-induced cell swelling (Eggermont et al. 2001; Sardini et al. 2003). In pancreatic β-cells, several lines of evidence, most of which have been reported by Best and co-workers (see review by Best et al. 2010), suggest that VRAC activated during RVD could also be an important mechanism for GSIS: (i) osmotic cell swelling activates VRAC in β-cells (Kinard and Satin 1995; Best et al. 1996b; Drews et al. 1998); (ii) glucose activates $Cl^-$ currents with features resembling VRAC currents (Best 1999; Best 2002b; Jakab et al. 2002); and (iii) both the glucose-activated $Cl^-$ currents and the swelling-induced insulin release are inhibited by a selective VRAC inhibitor DCPIB (Best et al. 2004). Since equilibrium potential of $Cl^-$ has been shown to be around −30 mV (Kinard and Satin 1995; Drews et al. 1998), the activation of VRAC would induce inward current, leading to membrane depolarization. However, the physiological role of VRAC besides RVD in β-cells is not fully understood. Recently, the non-metabolizable analogue 3-*O*-methylglucose as well as glucose has been shown to induce VRAC currents (Dossena et al. 2011), implying that the activation of VRAC by glucose may be independent of glucose metabolism.

### 14.2.4 Stretch-Activated Cation Channels

Osmotic cell swelling mechanically stretches the plasma membrane. It is thus expected that stretch-activated cation channels (SAC) participate in the responses to hypotonic stimulation in β-cells. However, little information exists about SAC in β-cells. In isolated rat pancreatic β-cells, we have demonstrated that hypotonic stimulation induces membrane depolarization, produces outwardly rectifying cation currents, and increases insulin secretion, and that all these responses are sensitive to relatively low concentration of $Gd^{3+}$ (Takii et al. 2006). The hypotonicity-induced insulin secretion was also inhibited by other cation channel blockers, such as amiloride, 2-APB, and ruthenium red (Takii et al. 2006). We have also obtained similar results in mouse pancreatic β-cells (Ishikawa, unpublished data). Thus, SAC is also suggested to be involved in the insulin secretion induced by β-cell swelling.

In other cell types, some transient receptor potential (TRP) channels are proposed as candidates of SAC. The TRP superfamily is one of the largest families of cation channels and subdivided into major branches; TRPC, TRPA, TRPM, TRPP, TRPV, TRPML, and TRPN (Nilius et al. 2007). There is increasing evidence that numerous TRP channels are expressed in β-cells, i.e., TRPC1-6, TRPM2-5, and TRPV1, 2, 4 (Islam 2011; Jacobson and Philipson 2007). These channels allow for β-cells to respond to a variety of stimulations including glucose, leading to membrane depolarization, $[Ca^{2+}]_c$ elevation, insulin secretion, cell survival, and apoptosis. At least ten mammalian TRPs have been suggested to exhibit mechanosensitivity, i.e., TRPC1, 5, and 6; TRPV1, 2, and 4; TRPM3 and 7; TRPA1; and TRPP2 (Inoue et al. 2009). Since the $[Ca^{2+}]_c$ elevation induced by hypotonic stimulation was sensitive to relatively low concentrations of ruthenium red in β-cells isolated from rats (Takii et al. 2006) and mice (Ishikawa, unpublished data), ruthenium red-sensitive channels, i.e., TRPV family or TRPA1, may be involved in the hypotonicity-induced responses. Among them, TRPV4 is a good candidate of SAC in β-cells. A recent study in the mouse β-cell line MIN6 has shown that human islet amyloid polypeptide (hIAPP) triggers $[Ca^{2+}]_c$ elevation, which corresponded with the appearance of hIAPP aggregates, alterations in the surface membrane morphology of MIN6 cells, and a reduction of cell viability. Small interference RNA against TRPV4 prevented hIAPP-induced $[Ca^{2+}]_c$ rises and reduced hIAPP-triggered cell death. It is thus suggested that TRPV4 may sense physical changes in the plasma membrane induced by hIAPP aggregation (Casas et al. 2008). Another candidate may be TRPV2. In MIN6 cells, TRPV2 has been shown to be translocated from the cytosol to the plasma membrane by insulin and participate in GSIS (Hisanaga et al. 2009). However, there is no indication how gating of TRPV2 is modulated in β-cells. Further studies are necessary to determine the molecular identity of SAC activated by cell swelling in β-cells.

### 14.2.5 Perspectives

There is increasing evidence that insulin secretion is not exclusively dependent on the $K_{ATP}$ channel-dependent mechanism. β-Cell swelling induced by high-concentration

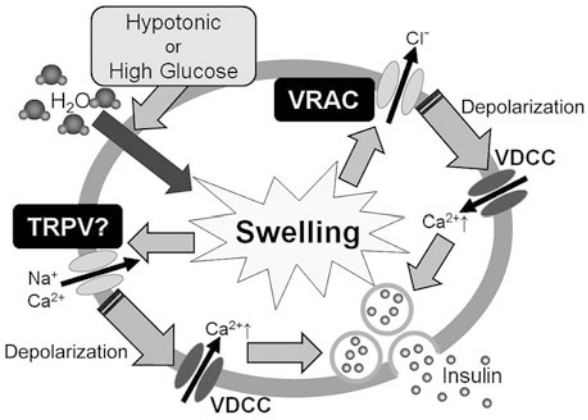


**Fig. 14.1** Mechanisms for β-cell swelling-induced insulin secretion. β-Cell swelling activates volume-regulated anion channels (*VRAC*) and/or stretch-activated cation channels, possibly TRPV, thereby causing membrane depolarization and subsequent activation of voltage-dependent $Ca^{2+}$ channels (VDCC), thus elevating insulin secretion

glucose may be one aspect of the $K_{ATP}$ channel-independent mechanism. The regulation of cell volume is important in β-cells, in which high rates of glucose metabolism increase intracellular osmolality. The involvement of VRAC in the membrane depolarization and insulin secretion induced by β-cell swelling has been extensively studied; however, several reports have argued against this proposition by showing that hypotonicity-induced insulin secretion persists even in the presence of $Cl^-$ channel blockers such as niflumic acid and DIDS (Kinard et al. 2001; Straub and Sharp 2002; Takii et al. 2006). Thus, the possibility still remains that mechanisms independent of VRAC are involved in the osmotic insulin secretion. Another potential candidate is mechanosensitive TRP channels; however, information available on them is limited (Fig. 14.1).

One major reason for this is the lack of specific inhibitors for TRP channel isoforms. Their study would be facilitated through RNA interference in cell culture and global mouse knockouts. Future studies with these techniques will elucidate the role of mechanosensitive TRP channels in $K_{ATP}$ channel-independent GSIS as well as β-cell swelling-induced insulin secretion.

## 14.3 Adipocyte

### *14.3.1 Introduction*

Recent advances in adipocyte research have established that adipose tissue not only serves as a means of energy storage in the form of triglycerides but also exerts secretory/endocrine functions. Adipocytes are the major cellular component of parenchymal adipose tissue, and are mesoderm or neuroectoderm in origin. The differentiation and hypertrophy (maturation) of adipocytes are fundamental processes involved in obesity. Mechanical stimuli such as stretching and rubbing of fat and skeletal muscle during gymnastic exercise or massage are believed to decrease

obesity as well. It is now considered that adipocytes are well equipped with possible candidates for mechanosensor molecules. These include chloride channels (Inoue et al. 2010) and TRP channels (Zhang et al. 2007), caveolae (Parton and Simons 2007; Pilch et al. 2007), kinases, including Rho-kinase (Hara et al. 2011), and focal adhesion proteins as well as stress fibers (Hara et al. 2011). In this regard, there have been quite a few papers as to the mechanosensitivity of adipocytes, i.e., how adipocytes respond to mechanical stimuli. Furthermore, adipocytes play a pivotal role in the secretion of hormones and cytokines/adipokines. Obese and matured adipose tissues produce a variety of proinflammatory adipokines, causing chronic inflammation. It has become clear that this obesity-induced chronic inflammation plays a key role in the development and progression of metabolic syndrome, including type-2 diabetes, hypertension, and pernicious obesity. Here, we present an overview of how adipocytes respond to mechanical stimuli with particular reference to the cell differentiation and the functions of secretory/endocrine gland, as well as adipose tissue inflammation, and their pharmacological interventions.

## *14.3.2 How does Mechanical Stress Act on Differentiation of Adipocytes?*

### 14.3.2.1 Cyclic Stretching

Maturation of adipocytes can occur all throughout life irrespective of age from the pre-existing cluster of adipoprogenitor cells (preadipocytes). Thus both the proliferation and differentiation of preadipocytes into mature adipocytes are issues of particular importance from a pathophysiological point of view.

Tanabe et al. (2004) first reported the effect of cyclic stretching on adipocyte differentiation. The optimum cyclic stretching with a frequency of 1 Hz was applied to 3T3-L1 cells in the induction medium for 45 h (induction period) while undergoing adipocyte differentiation. After 45 h of induction, the cells subjected to cyclic stretching were oriented perpendicular to the axis of stretching. Thus, uniaxial stretching induces a phenotypic change in cytoskeletal structures of adipocytes, similar to that often observed in vascular endothelial cells subjected to hemodynamic forces such as blood pressure and blood flow. Furthermore, Oil-Red-O staining revealed that the accumulation of lipid droplets was significantly inhibited in the 3T3-L1 cells subjected to cyclic stretching.

As to the molecular mechanism of adipocyte differentiation, at least three members of CCAAT-enhancer-binding proteins (C/EBP) family (C/EBPα, β, and δ) and the $\gamma$-isoform of the peroxisome proliferator-activated receptor (PPAR) family (PPAR$\gamma$1 and $\gamma$2) play pivotal roles in the regulation of adipipocyte differentiation, in particular, from preadipocyte to mature adipocyte (Rangwala and Lazar 2000; Rosen and Spiegelman 2000). Only the application of cyclic stretching during the late phase of induction could inhibit the adipocyte differentiation of 3T3-L1 cells, which was accompanied by the downregulation of PPAR$\gamma$1 and $\gamma$2 without any change in the expression of mRNA transcript for C/EBP (Tanabe et al. 2004).

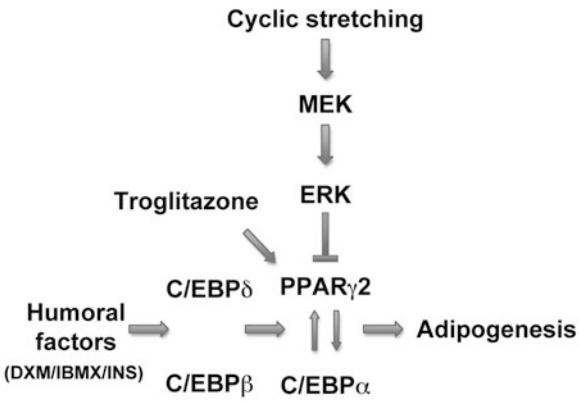


**Fig. 14.2** Schematic diagram indicating inhibitory effect of cyclic/dynamic stretching on the process of differentiation involved in adipogenesis. Note that adipocyte differentiation is inhibited by mechanical stretching through ERK-mediated downregulation of a transcription factor PPAR$\gamma$2. Troglitazone, a thiazolidinedione, accelerates the differentiation process, while cyclic stretching counteracts the process. (See in detail Tanabe et al. (2004))

#### 14.3.2.2 MEK/ERK Pathway and Rho/Rho-Kinase Activity

Several lines of evidence have suggested that mechanical stimuli evoke the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK/ERK) pathway in various types of cells (Tibbles and Woodgett 1999; Yamboliev et al. 2000). The stretch-induced blockade of adipocyte differentiation was reversed by PD98,059, an inhibitor of MEK, with concomitant restoration of the expression of PPAR$\gamma$2 at the mRNA and protein levels. In contrast, the expression of PPAR$\gamma$1 mRNA, which was reduced in response to the stretching condition, was not restored by PD98,059. PD98,059 also restored lipid droplet accumulation. Furthermore, the differentiation inhibited by stretching was also restored by a synthetic PPAR$\gamma$ ligand such as troglitazone. Therefore, inhibition of adipocyte differentiation in response to cyclic stretching is mainly attributable to the reduced expression of PPAR$\gamma$2, which is negatively controlled by activation of the MEK/ERK system (Fig. 14.2).

Mechanical stress also activates Rho/Rho-kinase and the subsequent signaling. Hara et al. (2011) investigated whether activation of Rho/Rho-kinase in adipose tissue participates in the development of obesity. 3T3-L1 cells were subjected to direct application of static mechanical stretching for a 72-hour duration. Rho-kinase activity and stress fiber formation were increased as lipid accumulated and cells swelled after the differentiation into adipocytes. Rho-kinase activation induces the expression of cytokines and chemokines that are adipocytic in origin such as tumor necrosis factor α (TNFα) and monocyte chemotactic activating factor 1 (MCP-1). Consistently, mature adipocytes were abundant in the mRNA transcripts encoding TNFα and MCP-1.

#### 14.3.2.3 Dynamic and Static Stretching

Shoham et al. (2012) have reported that static mechanical stretching at the static tensile strains of 12 % to the substrata accelerates lipid production in 3T3-L1 adipocytes

by activating the MEK pathway. Thus, the input pathway of static mechanical stretching seems to be similar to that of cyclic stretching. However, a PPAR$\gamma$ inhibitor, GW 9662, had no apparent effect on the adipocyte differentiation, indicating an alternative signaling pathway not yet revealed may be involved in the adipocyte differentiation.

It is considered that dynamic/cyclic stretching more effectively activates electrical and subsequent events than static stretching (Johansson and Mellander 1975). For instance, in vascular smooth muscle, the dynamic stretching mobilizes both extra- and intracellular-activator $Ca^{2+}$, while the static one promotes mainly influx of $Ca^{2+}$ through L-type $Ca^{2+}$ and other ion channels (Obara et al. 2001; Nakayama et al. 2010). Thus it appears possible that static and dynamic stretching evokes different cell signaling in adipocytes. However, as to mechanical stress in adipose cells and tissues, one needs to be careful when interpreting the results obtained. Although confluent cultures of 3T3-L1 cells undergo differentiation into adipocytes with or without stretching, this "without stretching" means that static tensile strain somehow always exists on the cell surface even when adipocytes are cultured on the surface of substrate. 3T3-L1 cells accumulate lipid droplets without any intentional procedure for stretching in the mature phase. Accordingly, Hara et al. (2011) have proposed a scheme depicting the vicious cycle of adipose tissues in obesity. The lipid deposition evokes adipocyte hypertrophy leading to further stretched cell membrane. Mechanical stretching and possibly some additional factors promote Rho-kinase activity, which contributes to both adipokine expression and recruitment of inflammatory cells, including macrophages, to adipose tissues. In turn, the chronic low-grade inflammatory process is accelerated (chronic inflammation), and lipid is further accumulated in a vicious cycle manner. It presumes that this vicious cycle of adipose tissue can take place only when adipocytes and surrounding tissues are properly adhered to each other for expanding (Fig. 14.3). The appropriate interaction between the cellular and extracellular matrix along with proper angiogenesis are particularly important for the development of adipose tissue *in vivo* (Han et al. 2011). As the developed network of blood vessels also nourishes the inflated-adipose tissues filled with lipid, it may be said that the state of chronic inflammation *in vivo* is caused by adipose tissues in concert with vascular tissues (adipogenesis-angiogenesis interaction) (Manabe 2011). Thus, hypertrophied adipose tissues together with an invading network of blood vessels and immune cells *in vivo* induce much more dysregulated production of proinflammatory mediators relative to the production of anti-inflammatory adipokines (e.g., adiponectin), which leads to adverse metabolic and cardiovascular consequences.

### *14.3.3 Mechanical Stress and Endocrine Function of Adipose Tissues*

It is a well-documented fact that adipocytes/adipose tissue function as the largest secretory organs in the whole body. *In vivo*, the clusters of small size adipocytes under non-inflammatory conditions primarily secrete adiponectin, pref-1, and other anti-inflammatory and anti-obese factors such as leptin. However, mature and

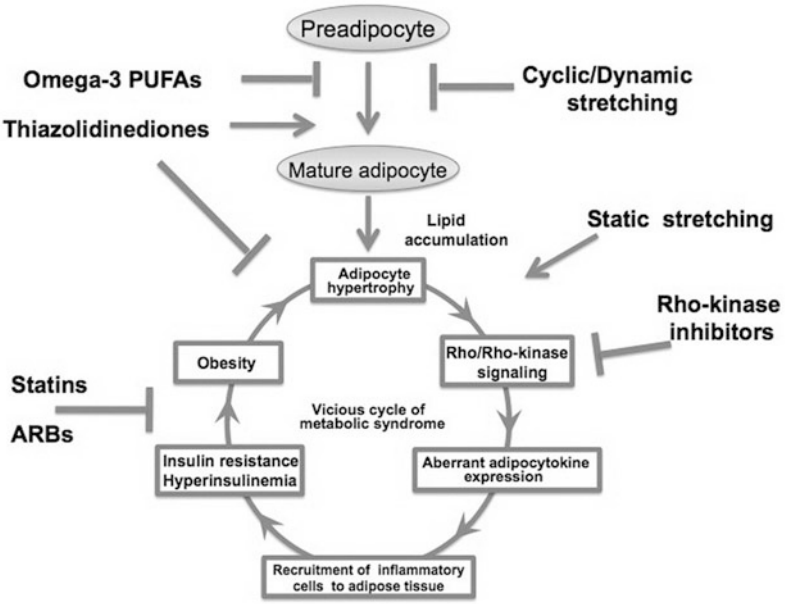


**Fig. 14.3** Possible inhibitory actions of several cardiovascular drugs on vicious cycle of adipose tissues in obesity. Once adipocyte has matured, it begins to accumulate lipid in the cell, leading to hypertrophied adipocyte, and stretching of surface membrane. Mechanical stretching together with other factors activates Rho/Rho-kinase signaling and subsequent proinflammatory processes including expression of adipocytokines, recruitment of macrophages, and vascular invasion, which further accelerate systemic insulin resistance, hyperinsulinemia, and obesity. This vicious cycle contributes to the progress of metabolic syndrome and further complicates obesity. Cyclic stretching in combination with several drugs such as Rho-kinase inhibitors, statins, and angiotensin $AT_1$ receptor blockers (*ARBs*), may interrupt this vicious cycle

fat-accumulated adipocytes (large adipocytes) induce the expression of cytokines and chemokines that are adipocytic in origin such as tumor necrosis factor (TNFα) and MCP-1. The secreted chemokine recruits immune cells such as M1 macrophages, T cells and neutrophiles. Moreover, vascular networks invaded by the cluster of mature adipocytes further propagate inflammatory cascades, leading to a state of chronic inflammation responsible for systematic insulin resistance and other metabolic abnormalities (Nishimura et al. 2008; Manabe 2011). Thus, in order to clarify the effect of mechanical stress on the adipocytic endocrine function, i.e., how mechanical stress acts directly and locally on adipose tissues *in vivo*, it is inevitably necessary to carry out long-term experiments in conscious animals *in vivo*.

#### 14.3.3.1 Rho/Rho-Kinase-Dependent Endocrine Function in Diet-Induced Obesity

Hara et al. (2011) reported that mice fed a high-fat diet showed increased adipocyte size, Rho-kinase activity, and stress-fiber formation in adipose tissue, as well as body

weight gain compared to mice fed a low-fat diet. Abundance of the mRNA transcripts encoding the adipocytokines TNFα and MCP-1 increased in adipose tissue of mice fed a high-fat diet. Conversely, abundance of the mRNA encoding adiponectin was decreased in mice fed a high-fat diet. Rho-kinase activity was increased after stretching in mature adipocytes. Furthermore, the expression of the mRNA transcripts encoding TNFα and MCP-1 was increased, whereas that encoding adiponectin was decreased. Fasudil and Y-27362, Rho-kinase inhibitors, reduced lipid accumulation and Rho-kinase activity in the mature cells. These are consistent with the *in vivo* data obtained in the diet-induced obese mice and dominant negative-RhoA transgenic mice. It is thus likely that lipid accumulation in adipocytes activates Rho/Rho-kinase signaling at least in part through mechanical stretching and implicates Rho/Rho-kinase signaling in adipose tissue in obesity.

#### 14.3.3.2 Local Vibration and Metabolic and Endocrine Functions of Adipocytes

We have investigated *in vivo* effects of mechanical vibration on adipose tissues in conscious mice. Male ddY mice fed a high-fat diet and weighing about 50 g received mechanical vibration (100 Hz for 30 min) on the lower abdomen twice a day for up to 16 days. The daily abdominal vibrations significantly lowered triglyceride content in adipose tissues and plasma concentration of free fatty acids without any changes in body weight, daily food intake, or plasma concentration of corticosterone, a stress maker. Moreover, the vibrations decreased expression of adipogenic transcription factors such as PPAR$\gamma$2 and sterol-regulatory element-binding protein-1c (SREBP-1c), while the expression of anti-adipogenic preadipocyte factor Pref-1 was increased. The increased Pref-1 is expected to induce a lowering of triglyceride content and the downregulation of adipokines such as leptin, resistin, and adiponectin in the epidermal adipose tissues, leading to a decrease in nonesterified fatty acids (NEFAs) in blood plasma. Thus, the daily abdominal vibrations can affect gene expression, endocrine, and metabolic function of adipose tissues, which would lead to a beneficial effect on obese-related diseases. However, the local vibration also induced the expression of pro-inflammatory genes; arginase-1, interleukin-10 (IL-10), and colony-stimulating factor Mgl-1, which are characteristic to M2 macrophages (alternatively-activated macrophages), and IL-6, IL-1β, MCP-1, and COX2, which are characteristic to M1 macrophages (classically-activated macrophages). Thus, mechanical stress such as vibration in combination with anti-inflammatory pharmacological interventions as mentioned below could improve the balance between proinflammatory factors and anti-inflammatory ones.

### *14.3.4 Mechanical Stress and Pharmacological Interventions*

Metabolic syndrome is considered to be a kind of chronic inflammatory state. Of the many cardiovascular drugs, several drug groups can also be used against proinflam-

matory processes often encountered in metabolic syndrome including hypertension and obesity. They include inhibitors of Rho/Rho-kinase, fasudil and Y-2736, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), ω-3 poly-unsaturated fatty acids, thiazolidinediones (TZDs), insulin-sensitizers, angiotensin $AT_1$ receptor blockers (ARBs), and HMG-CoA reductase inhibitor statins.

#### 14.3.4.1 Rho/Rho-Kinase Inhibitors

Rho/Rho-kinase and subsequent signaling might be activated by stretching cell membrane when mature adipocytes become hypertrophic in obesity (Hara et al. 2011). Direct application of static stretching to mature adipocytes increased the expression of the mRNA transcripts encoding TNFα and MCP-1 and stress fiber formation, whereas the expression of the mRNA encoding adiponectin was decreased. These changes in mRNA abundance were inhibited by the Rho-kinase inhibitor Y-27632 or fasudil. Thus, lipid accumulation in adipocytes is likely to activate Rho/Rho-kinase signaling, at least in part, through mechanical stretching. The activated signaling further accelerates inflammatory changes in adipose tissue in obesity in a vicious cycle manner. This vicious cycle could be interrupted by the Rho-kinase inhibitors, which may provide a novel therapeutic strategy for obesity and related diseases, including insulin resistance and atherosclerosis (Hara et al. 2011) (See Fig. 14.3).

#### 14.3.4.2 ω-3 Polyunsaturated Fatty Acids, EPA and DHA

A variety of endogenous and exogenous lipids and fatty acids play an important role in adipocyte differentiation. EPA and DHA are fish-oil-derived ω-3 polyunsaturated fatty acid (PUFA) possessing a variety of pharmacological actions, including antithrombic, anti-inflammatory, anti-atherogenic, and antiarrhythmic activities (Kris-Etherton et al. 2002; Holub and Holub 2004). Furthermore, ω-3 PUFA modulates gene expression involved in lipid homeostasis in adipocytes. When EPA was concomitantly applied with cyclic stretching, adipocyte differentiation was significantly reduced, although EPA alone had no effect on the differentiation (Tanabe et al. 2008). EPA could be a substrate of COX2, the expression of which was strongly augmented by stretching. A selective COX2 inhibitor NS-398 attenuated the combined effect of stretching and EPA. Thus, stretching and EPA are suggested to exhibit a synergistic effect on the inhibition of adipocyte differentiation through stretch-induced COX2 production. In contrast, DHA is not a direct substrate for either COX1 or COX2 (Hirafuji et al. 2003), indicating no apparent synergistic effects with stretching.

#### 14.3.4.3 PPAR$\gamma$ Agonist Thiazolidinediones

Thiazolidinediones (TZD) are agonistic ligands for peroxisome proliferator-activating receptor $\gamma$ (PPAR$\gamma$), a group of nuclear hormone receptors. The activated

receptor migrates to the DNA, which is involved in the regulation of genes related to glucose and lipid metabolism. PPAR$\gamma$ agonists have been reported to possess anti-inflammatory activity, suggesting their possible use for treatment of inflammatory and autoimmune diseases (Straus and Glass 2007). One of the adverse actions of TZD is obesity due to a decrease in leptin levels and an acceleration of adipocyte differentiation. Cyclic stretching inhibited the accelerating action of TZD on the adipocyte differentiation assessed in 3T3-L1 cells (Tanabe et al. 2004). TZD also shows anti-inflammatory action by increasing adiponectin and by decreasing certain interleukins, e.g., IL-6, and vascular endothelial growth factor (VEGF)-induced angiogenesis. Thus, mechanical stretching may ameliorate the adverse action of TZD in obesity and enhance the pleiotropic action of TZD in the therapy of type2 diabetes (Tanabe et al. 2004).

#### 14.3.4.4 $AT_1$ Receptor Blockers and Statins

Angiotensin II (AngII) type 1 receptor ($AT_1R$), a GTP binding protein-coupled receptor (GPCR), plays a crucial role in the regulation of cardiovascular homeostasis. In addition to circulating and local AngII, evidence has accumulated that mechanical stress including high blood pressure can activate $AT_1R$ and induces cardiac hypertrophy (Zou et al. 2004; Yasuda et al. 2008) and vascular myogenic contraction (Voets and Nilius 2009). The mechanical strain is transmitted via Gq proteins coupled to $AT_1R$ (Akazawa and Komuro 2010) or other adaptor proteins such as β-arrestins (Rakesh et al. 2010). The agonist-independent activation of $AT_1R$ can be inhibited by inverse $AT_1R$ agonists such as candesartan and olmesartan (Miura et al. 2006). $AT_1R$ blockers (ARBs) substantially lower the risk for type 2 diabetes, and improves insulin sensitivity in animal models of insulin resistance. A specific subset of ARBs such as telmisartan and irbesartan has been shown to stimulate PPAR$\gamma$ activity independently of their $AT_1R$ blocking actions (Schupp et al. 2004). The pleiotropic effects of ARBs including blocking the action of mechanical stress emerge as an important pharmacological characteristic for $AT_1R$ and other GPCRs, which determine the efficacy to protect tissue and cells against cardiovascular and metabolic diseases.

The HMG-CoA reductase inhibitor statins have been clinically used to slow down the progression of atherosclerosis by inhibiting the rate-limiting step of biosynthesis of cholesterol. However, statins are now also shown to possess non-lipid lowering benefits, i.e., pleiotropic actions (Lefer 2002). The pleiotropic effects of statins have been often argued to occur in cardiovascular tissues. Pravastatin and rivastatin act inhibitory on the adipose tissue inflammation and toll-like receptor-4 (TLR4)-mediated signaling in macrophages (Abe et al. 2008). However, some statins including atorvastatin inhibited adipocyte maturation and expression of glucose transporter 4 (GLUT4).

There is so far no information available as to the effect of mechanical stretching in combination with statins on glycemic control in adipocytes. It would be important to recognize obesity, which is a crucial cause of metabolic syndrome, as a chronic inflammatory disease and to fully clarify how pharmacological interventions toward

cardiovascular and metabolic diseases in combination with mechanical stress act on adipose tissues *in vivo*.

### *14.3.5 Perspectives*

It has become clear that the intercommunication between the central nervous system and peripheral organs, including pancreatic β-cells, adipocytes, and skeletal muscle cells is important for the maintenance of homeostasis in energy-glucose metabolism (Devaskar 2001; Sandoval et al. 2009). This intercommunication has often been discussed from the view point of the neurohumoral axis. However, the intercommunication among these peripheral organs is also important. The balance of anti- and pro-inflammatory cytokines, for instance, adiponectin and plasminogen-activator inhibitor-1 (PAI-1), respectively, released from adipocyte by mechanical and other stimuli also strongly affects not only insulin secretion but also the sensitivity of adipocyte and skeletal muscle cells to insulin (Corgosinho et al. 2011; Lumeng and Saltiel, 2011). Moreover, the adipogenesis coupled with vascular angiogenesis (Nishimura et al. 2008; Manabe 2011), an alternative kind of intercommunication, plays a pivotal role in the process of chronic inflammation and metabolic syndrome.

## 14.4 Skeletal Muscle

### *14.4.1 Introduction*

The skeletal muscle is the main tissue involved in glucose disposal *in vivo*, and its function is exquisitely regulated by several stimuli including muscle contractions and insulin (Holloszy 2003). The major cellular mechanism for disposal of an exogenous glucose load is glucose transport into skeletal muscle. The principal glucose transporter protein in skeletal muscle is GLUT4, which is one isoform of glucose transporter proteins containing 12-transmembrane domains. Muscle contraction and insulin increase the glucose transport which can be rapidly induced by translocation of GLUT4 from intracellular vesicles to the plasma membrane and/or transverse tubules (T-tubules) (Dombrowski et al. 1996; Holloszy 2003) and possibly by increased intrinsic activity of GLUT4 (reviewed in Furtado et al. 2003). The GLUT4 translocation induced by muscle contraction and insulin is mediated by distinct signaling pathways, and their maximal effects on muscle glucose uptake are additive (Holloszy 2003). GLUT4 is thus a major mediator of glucose removal from the circulation and a key regulator of whole-body glucose homeostasis.

Muscle contraction is accompanied by mechanical stimuli such as passive stretching or deformation of cells and tissues. Stretching of skeletal muscle results in changes in cellular metabolism, including glucose transport (Ihlemann et al. 1999; Ito et al. 2006). Indeed, mechanical stretching per se has been reported to increase the glucose transport in skeletal muscle without force-producing contraction (Ihlemann

et al. 1999; Ito et al. 2006), as well as in cultured L6 (Mitsumoto et al. 1992) and C2C12 myotubes (Iwata et al. 2007). We have further shown that passive stretching induces the translocation of GLUT4 only to the plasma membrane, but not to T-tubules, in rat skeletal muscle, whereas active contraction and insulin stimulate the translocation of GLUT4 to both the plasma membrane and T-tubules (Ito et al. 2006). Thus, passive stretching is likely to play a major role in skeletal muscle glucose transport. However, there is still controversy as to which intracellular signaling pathways that mediate the effects of mechanical stretching on glucose transport.

### *14.4.2 Mechanosensors in Skeletal Muscle*

Many molecules have been proposed as a mechanosensor in skeletal muscle, including SAC (Spangenburg and McBride 2006) and integrins (Zanchi and Lancha 2008); however, none of them are definitive. Skeletal muscle may have multiple mechanosensors, which all integrate the mechanical information into anabolic or catabolic responses.

#### 14.4.2.1 Stretch-Activated Channels (SAC)

SAC was first discovered by patch clamping in skeletal muscle (Guharay and Sachs 1984), but the molecular identity of the channel is still unknown. SAC in skeletal muscle is permeable to $Ca^{2+}$ as well as $Na^{+}$ (Franco and Lansman 1990) and activated by stretching of the membrane. TRP channels are a good candidate to account for SAC. Several members of the TRPC, TRPV and TRPM subfamilies are expressed in skeletal muscle. The most prominent TRP channels are TRPC1, C3, C4 and C6, TRPV2 and V4 as well as TRPM4 and M7. TRPC1 is well characterized TRP in skeletal muscle, and can be activated by membrane stretching (Maroto et al. 2005). Even though many studies point to TRPC1 as being a stretch-activated channel (Ducret et al. 2006), this topic remains controversial, with tissue-specific investigations of TRPC1 function often providing negative results (Dietrich et al. 2007).

#### 14.4.2.2 Integrin

There is increasing evidence indicating that integrin plays an important role in mechanotransduction (Sasamoto et al. 2005). Integrin is a heterodimeric complex composed of α and β subunits. There are 19α and 8β mammalian subunit isoforms (Humphries 2000). In skeletal muscle, integrin is limited to seven subunit subtypes, i.e., α1, α3, α4, α5, α6, α7, and αv subunits, all associated with β1 subunit (Schwander et al. 2003). Recently, we found that stretch-induced glucose uptake is inhibited by JB1 A, an integrin β1 blocking antibody (Ni et al. 1998), in cultured L6 myotubes

(Obara et al., unpublished observation), suggesting the involvement of integrin in stretch-induced glucose uptake into skeletal muscle.

### *14.4.3 Possible Mediators of Mechanotransduction*

Iwata et al. (2007) have shown that mechanical stretch-stimulated glucose uptake is insensitive to wortmannin, an inhibitor of phosphoinositide 3-kinase (PI3K), whereas the effect of insulin is completely abolished by the PI3K inhibitor. These results suggest that the stretch signaling pathway mediates skeletal muscle glucose uptake through a pathway independent of insulin. Passive stretching of skeletal muscle is suggested to mimic the effects of muscle contractions on cellular metabolism, including glucose uptake (Ihlemann et al. 1999). It is thus hypothesized that the stimulation of glucose uptake by mechanical stretching may be mediated by pathways similar to those stimulated by contractions/exercise.

#### 14.4.3.1 AMP-Activated Protein Kinase

AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase activated by various stresses leading to the depletion of cellular ATP (Hardie et al. 1998). AMPK consists of one catalytic subunit (α) and two noncatalytic subunits (β, $\gamma$). AMPK is proposed to be a key mediator of glucose uptake into skeletal muscle during contractions and exercise. The α2-containing complex of AMPK is the primary catalytic isoform and activated during exercise (Musi et al. 2001; Wojtaszewski et al. 2000). The pharmacological activator of AMPK, adenosine analogue 5-aminoimidazole 4-carboxamide ribonucleoside (AICAR), can increase glucose uptake (Hayashi et al. 1998). However, there is apparent disassociation between AMPK activation and glucose uptake during exercise (Derave et al. 2000). Moreover, AMPK α2 knockout abolishes AICAR-induced glucose uptake, but has no inhibitory effect on contraction-induced glucose uptake (Jørgensen et al. 2004). Thus, it is likely that AMPK has the ability to increase glucose uptake, but is not essential for contraction-stimulated glucose uptake. AMPK is also unlikely to be involved in the stimulation of glucose uptake by mechanical stretching. In cultured C2C12 myotubes, compound C, an inhibitor of AMPK, completely inhibited the glucose transport induced by AICAR but not that induced by stretching (Iwata et al. 2007). This notion is also supported by our observation that mechanical stretching has no apparent effect on AMPK activity in mouse skeletal muscle *in vitro* (Ito et al. 2006).

#### 14.4.3.2 $Ca^{2+}$ and $Ca^{2+}$/Calmodulin-Dependent Protein Kinase

The experiments with caffeine, which induces release of $Ca^{2+}$ from sarcoplasmic reticulum (SR) of isolated skeletal muscle without membrane depolarization, have

shown that raising $[Ca^{2+}]_c$ increases glucose uptake (Holloszy and Narahara 1967). Studies from several groups have shown that increases in $[Ca^{2+}]_c$ during skeletal muscle contraction provide the signal leading to contraction-induced increases in glucose transport (Holloszy and Narahara 1967; Clausen et al. 1975; Wijesekara et al. 2006). This possibility is supported by the observation that a $Ca^{2+}$ ionophore ionomycin or ryanodine, which elicits the release of $Ca^{2+}$ from SR, induces glucose uptake into C2C12 myotubes accompanied by an elevation of $[Ca^{2+}]_c$ below the contraction threshold (Iwata et al. 2007).

Cyclic stretch-dependent $Ca^{2+}$ influx is suggested to be essential in several stretch-dependent signal transductions (Inou et al. 2002; Wang et al. 2001). In contrast, intracellular $Ca^{2+}$ stores seem also to serve as a mechanotransducer in the stretch-induced signaling pathway in multiple cell types (Taskinen and Ruskoaho 1996). The stretching of C2C12 myotubes has been shown to induce a rapid increase in $[Ca^{2+}]_c$ (Iwata et al. 2007). The depletion of extracellular $Ca^{2+}$ did not affect the glucose uptake induced by cyclic stretching and the inhibition of $Ca^{2+}$ release from intracellular $Ca^{2+}$ storage sites completely prevented stretch-stimulated glucose uptake in C2C12 myotubes (Iwata et al. 2007) and in mouse soleus muscle (Obara unpublished observation).

$Ca^{2+}$/calmodulin-dependent protein kinases (CaMK) are activated by $Ca^{2+}$ (Soderling 1999), and CaMK is involved in the stimulation of muscle glucose uptake (Chin 2005). The inhibition of CaMK by KN93, a specific inhibitor of CaMK (Sumi et al. 1991; Corcoran and Means 2001), leads to a decrease in the glucose transport stimulated by cyclic stretching in C2C12 myotubes (Iwata et al. 2007) and by contraction in rodent skeletal muscles (Wright et al. 2004). These findings suggest that stretch-stimulated glucose transport appears to be dependent on the $Ca^{2+}$/CaMK signaling pathway. Three CaMKs, i.e., CaMKI, CaMKII, and CaMKIV, are activated by $Ca^{2+}$, and all of the CaMKs are inhibited by KN93 (Corcoran and Means 2001). CaMKII, but not CaMKI or CaMKIV, is expressed in human skeletal muscle (Rose et al. 2006). The activation of CaMKII by $Ca^{2+}$ mediates the contraction-induced increases in glucose transport in rat epitrochlearis muscle (Wright et al. 2004). It is thus likely that stretch-stimulated glucose transport is mediated by the $Ca^{2+}$/CaMKII-dependent signaling pathway.

#### 14.4.3.3 Nitric Oxide

Nitric oxide (NO) is a gas synthesized by the enzyme nitric oxide synthase (NOS). Three NO synthase (NOS) isoforms, i.e., NOS1 (neuronal NOS; nNOS), NOS2 (inducible NOS; iNOS), and NOS3 (endothelial NOS; eNOS), have been described: NOS1 and NOS3 are constitutively expressed and $Ca^{2+}$/calmodulin-dependently activated, while the expression of NOS2 is induced by cytokines (Moncada et al. 1991). Several isoforms have been identified that result from alternative splicing of the nNOS gene. Of these nNOS isoforms, nNOSμ is the most prevalent isoform expressed in skeletal muscle fibers (Silvagno et al. 1996). The involvement of NO in glucose uptake into skeletal muscle is suggested by several lines of evidence: The

NO donor sodium nitroprusside (SNP) increases glucose uptake in skeletal muscle independently of insulin (Balon and Nadler 1997) and NOS inhibitors attenuate or abolish increases in glucose uptake during contractions in rodent skeletal muscle (Balon and Nadler 1997; Ross et al. 2007). Moreover, skeletal muscle contraction has been shown to increase cGMP formation (Lau et al. 2000), suggesting that NO increases contraction-induced glucose uptake via the NO/cGMP pathway. NO seems also to mediate glucose uptake induced by mechanical stretching as well as contractions. Cyclic stretching has been shown to increase nNOS expression and NO production (Tidball et al. 1998; Zhang et al. 2004), and to stimulate glucose uptake in C2C12 myotubes (Iwata et al. 2007). We have confirmed that $N^{G}$-nitro-L-arginine methylester (L-NAME), an inhibitor of NOS, inhibits glucose uptake induced by cyclic stretching in mouse soleus muscle (Obara, unpublished observation). NO is thus likely to mediate increased glucose uptake during cyclic stretching as well as during contraction. In this regard, identifying the pathways through which NO acts during mechanical stretching is still needed.

#### 14.4.3.4 p38 Mitogen-Activated Protein Kinase

A potential role of p38 mitogen-activated protein kinase (p38 MAPK) in the contraction- and insulin-stimulation of glucose transport in skeletal muscle is suggested (Somwar et al. 2000; 2002). Somwar et al. (2002) showed that p38 MAPK mediates an increase in glucose transport by activating GLUT4 although it is not involved in GLUT4 translocation to the cell surface. In adult rat skeletal muscle, exercise and contraction increase the phosphorylation and activity of multiple isoforms (α, β, and $\gamma$) (Goodyear et al. 1996). Of these isoforms, $\gamma$-isoform (p38 $\gamma$MAPK) is highly regulated by muscle contraction (Boppart et al. 2000). Recently, it has been reported that p38 $\gamma$MAPK decreases contraction-stimulated glucose uptake by affecting intrinsic GLUT4 activity in skeletal muscle of mice (Ho et al. 2004). Although we observed that total phosphorylation of p38 MAPK isoforms was increased by mechanical stretching in mouse skeletal muscle, it is possible that an isoform such as p38 $\gamma$MAPK may negatively regulate glucose uptake induced by passive stretching, resulting in a small glucose uptake despite large translocation of GLUT4 to the plasma membrane (Ito et al. 2006).

### *14.4.4 Perspectives*

Mechanical stretching increases skeletal muscle GLUT4 translocation from intracellular vesicles to the surface membrane and increases glucose uptake, but it is clear that insulin- and contraction-independent pathways are involved. The mechanisms by which mechanical stretching increases glucose uptake into skeletal muscle are not fully elucidated, but may involve $Ca^{2+}$/CaMKII, p38 MAPK, and NO signaling (Fig. 14.4). In addition, β1 subunit-containing integrins seem to locate upstream of the mechanotransduction cascade. It is likely that more than one pathway is involved

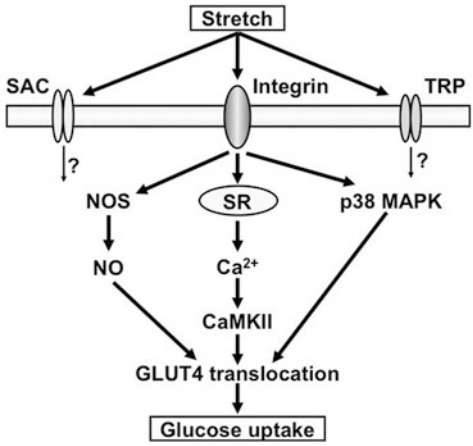


**Fig. 14.4** Possible mechanisms involved in stretch-induced glucose uptake. *SAC*, stretch-activated channel; *TRP*, transient receptor potential channel; *NOS*, nitric oxide synthase; *NO*, nitric oxide; *SR*, sarcoplasmic reticulum; p 38 MAPK, p 38 mitogen-activated protein kinase; CaMKII, $Ca^{2+}$/calmodulin dependent protein kinase type II; GLUT4, glucose transporter 4

in signaling of GLUT4 translocation and glucose uptake stimulated by mechanical stretching and that overlapping of pathways and redundancy may occur; if one pathway is inadequate or blocked, another pathway may be upregulated.

## 14.5 Conclusion and Perspectives

In this review, we have provided a brief review of currently available knowledge on the cellular and molecular mechanisms as to the mechanosensitivity of pancreatic β-cells, adipocytes and skeletal muscle cells. All of these cells and tissues play a critical role in the energy metabolism, and are related to a core concern in the metabolic syndrome. As has been well documented, skeletal muscle cells are always subjected to mechanical stress during muscle contraction such as exercise, and other various motions. However, as shown in this review, both β-cells and adipocytes are also quite mechanosensitive. In this regard, there are quite a few papers as to the mechanosensitive mechanisms of these cells and tissues. It has become clear that these cells and tissues react differentially in their functions when subjected to mechanical stress. It is now considered that the obesity-induced chronic inflammation is critical in the development and progression of metabolic syndrome. While research concerning pharmacological intervention and mechanosensitivity seems to be still in its infancy, we believe that further study of mechanosensitivity/mechanotransduction in cells and tissues, particularly that involved in the metabolic syndrome and cardiovascular complications, will aid in further recognizing the importance of biomechanical factors in physiological and pathophysiological conditions, and will open up a new era of novel therapeutic remedies.

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