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Role of β-adrenergic receptors in insulin resistance: Induction or protection?

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Brief running title: β-adrenergic receptors and insulin resistance

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Abstract

β-Adrenergic receptors (βARs), in particular β2-subtype, are key regulators of glucose homeostasis. Previous studies showed that activation of hepatic and adipose tissue βARs mediates insulin desensitizing effects. On the contrary, activation of βARs in the skeletal muscle enhances glucose uptake. However, there is a lot of controversy regarding the metabolic effects of systemic administration of either βAR agonists or antagonists. β2-Agonists have been shown to substantially impair glucose homeostasis while improving it with long-term systemic administration. In the same context, acute and chronic systemic use of certain types of β-blockers have been found to enhance insulin action. In this review article, we try to elaborate the underlying mechanisms that regulate glucose metabolism after acute and chronic systemic use of βAR agonists and antagonists in an attempt to answer the question "Do βARs induce or protect against insulin resistance?"

Keywords

β-Adrenergic receptors, insulin resistance, β-agonists, β-blockers, glucose homeostasis.

Introduction

β-Adrenergic receptors (βARs) belong to G-protein-coupled receptors (GPCRs) that bind to epinephrine and norepinephrine to mediate its physiological response **(Hall, 2004).** GPCRs are seven-transmembrane-spanning receptors that couple to the heterotrimeric G-protein complex (Gαβγ) **(Alexander et al., 2019)**. Activation of a GPCR induces a conformational change of the receptor and promotes guanosine diphosphate (GDP) exchange for guanosine triphosphate (GTP) via guanine nucleotide exchange factors causing dissociation of G-proteins into activated Gβγ- and Gα-proteins **(Rockman et al., 2002)**. Gα-proteins are further classified into four major different types: $G\alpha_S$, $G\alpha_i$, $G\alpha_q$, and $G\alpha_{12}$ **(Madamanchi, 2007)**.

βARs are also subdivided into three subtypes: β1AR is mainly found in the heart and brain **(Frielle et al., 1987)**, β2AR is more widely distributed **(Dixon et al., 1986)**, and β3AR is mainly found in adipose tissue **(Emorine et al., 1989)**. The three subtypes couple primarily to $G\alpha_s$ to stimulate adenylyl cyclase but can also couple to $G\alpha_i$ to inhibit adenylyl cyclase (AC) in some cells under certain conditions **(Daaka et al., 1997; Soeder et al., 1999; Xiang et al., 2002)**. Coupled to

Gαs, the βARs activate AC, cyclic adenosine monophosphate (cAMP) synthesis, and protein kinase A (PKA) activity **(Halls and Cooper, 2017)**.

In the heart, β1AR is 4-times more expressed than β2AR **(Cannavo et al., 2013)**. The expression of β3AR is very low in normal heart but it is upregulated during heart failure **(Moniotte et al., 2001)**. On the contrary, β1AR decreases during heart failure, while the expression of β2AR increases, reaching a ratio of 3:2 **(Bristow et al., 1986)**. Upon prolonged cardiac β1AR stimulation, the levels of β1AR at the plasma membrane decrease and $G\alpha_s$ becomes uncoupled from AC. This diminishes cAMP production, yet induces the activation of calcium/calmodulin kinase (CaMK)II, which promotes hypertrophy in cardiomyocytes **(Zhang et al., 2003; Tilley and Rockman, 2006)**.

Persistent cardiac β2ARs activation can cause coupling of the receptor to the $G\alpha_i$-pathway under the influence of G-protein-coupled receptor kinase (GRK) 2 and/or GRK5 and PKA and/or protein kinase C (PKC) phosphorylation **(Lefkowitz, 1998)**. This might opposes the positive inotropic effects mediated via $G\alpha_S$, which in turn, activates a cell survival pathway **(Communal et al., 1999)**.

In contrast to their clear roles in cardiac muscle activity, βARs' role in insulin resistance and glucose homeostasis is highly controversial. In this review, we discuss the different metabolic effects of βARs and try to resolve the controversy regarding their roles.

2. Insulin resistance

Insulin resistance is a condition where body cells become resistant to insulin effects, resulting in abnormally large amount of insulin to attain a normal biologic response **(Petersen and Shulman 2018)**. Indeed, the resistance occurs with both endogenous and exogenous insulin. Resistance to endogenous insulin in the muscle, fat, and liver cells is compensated by elevated serum insulin concentration accompanied with normal or increased glucose concentration **(Yaribeygi et al., 2019)**. Insulin resistance is the crucial causative mechanism of type II diabetes and is highly correlated with increased risk of hypertension, and cardiovascular diseases **(Wilcox, 2005)**.

Insulin resistance may be due to defects either before insulin binds to its receptor, at the level of the insulin receptor, or at a level beyond the downstream signaling.

Insulin receptor defect is generally caused by genetic mutations in the insulin receptor gene leading to defects in receptor number, structure, binding, affinity, or signaling capacity **(Haeusler et al., 2018; Melvin et al., 2018)**.

Post-insulin receptor defect is caused by several pathways that either mediate degradation of the insulin receptor substrate-1 (IRS-1) by serine phosphorylation, inhibition of insulin receptor-IRS-1 interaction, or inhibition of protein kinase B (Akt) serine 473 phosphorylation **(Shimobayashi et al., 2018)**. Free fatty acids can elevate intracellular diacylglycerol (DAG) level that mediates the activation of PKC and degradation of IRS-1 **(Wang et al., 2009; Nandipati et al., 2017; Palomer et al., 2018)**. In the same way, inflammatory cytokines promote PKC-activation/IRS-1 degradation and inhibit insulin receptor-IRS-1 interaction **(Wu and Ballantyne, 2017)**. On the other hand, β-arrestin2, a GPCR desensitizing and scaffolding protein, has been found to play a critical role in insulin signaling by mediating the interaction between IRS-1, Src and Akt to promote serine 473 phosphorylation of the latter **(Luan et al., 2009)**. Notably, β-arrestin2 is downregulated during type II diabetes, insulin resistance, and obesity **(Feng et al.,**

2011). Furthermore, feeding rodents high fat and high fructose diets has been found to downregulate β-arrestin2 in the classical insulin target tissues such as liver, skeletal muscle, and adipose tissue causing insulin resistance **(Zhu et al., 2017; El-Fayoumi et al., 2020)**.

Noteworthy, the insulin resistance progression to cardiovascular disease or type II diabetes can be divided into four stages. Stage I of insulin resistance is distinguished by craving to carbohydrates, mild insulin resistance, and gaining weight easily as increased amount of food energy (transformed into blood sugar) is directed to the liver, converted into blood fat, and then stored in fat cells **(Wurtman et al., 1981)**. Moreover, in stage I, a diet rich in carbohydrate (within 2 h) may result in irritability, tiredness, or poor concentration. Though, these signs and symptoms may differ among individuals. However, fasting levels of insulin and blood glucose remain within the normal range **(Reddy et al., 2010)**. Stage II of insulin resistance is characterized by normal or increased fasting insulin levels, normal blood glucose, mild-to-moderate central obesity, high blood pressure, early atherogenic dyslipidemia, vascular inflammation with elevated circulating levels of inflammatory markers, and endothelial dysfunction **(DeFronzo, 1997; Patil and Watve, 2010)**.

This is followed by stage III of insulin resistance, which is characterized by high fasting insulin levels, impaired glucose tolerance (prediabetes), advanced atherogenic dyslipidemia including increased lipoproteins containing apolipoprotein B, triglycerides, elevated small dense low-density lipoprotein (LDL) particles, and decreased levels of high-density lipoproteins (HDLs) and prothrombotic stage signifying anomalies in procoagulant factors, antifibrinolytic factors and platelet aberrations. Noteworthy, stage III of insulin resistance is collectively termed metabolic syndrome **(DeFronzo and Ferrannini, 1991; Fukushima et al., 2004)**.

In the 4th stage of insulin resistance, there is a complete resistance of body cells to insulin and this stage is marked by high levels of fasting insulin and blood glucose levels. Notably, stage IV is the first onset of frank type II diabetes mellitus and advanced atherosclerotic changes with strong potential for cardiovascular disease and its complications **(Reddy et al., 2010)**.

2.1 β-Adrenergic receptors and hepatic insulin resistance

Catecholamines, such as epinephrine and norepinephrine, can regulate liver metabolism by activating hepatic βARs and its coupled $G\alpha_s$ protein **(Dax et al., 1987; Katz et al., 1987; Arner et al., 1990)**. Both β1- and β2-ARs are expressed in the liver, and their expression increases with aging **(Arner et al., 1990)**. However, the hepatic level of β2AR is higher than β1-subtype. Activation of the βARs/$G\alpha_s$/AC pathway increases hepatic glucose output and liver lipid catabolism **(Aggerbeck et al., 1983; Erraji-Benchekroun et al., 2005; Ghosh et al., 2012)**. In rat hepatocytes, the activation of βARs with the nonselective agonist isoproterenol increases glycogen phosphorylase activity by many folds and decreases liver glycogen levels **(Erraji-Benchekroun et al., 2005)**. Moreover, the activation of hepatic βARs by isoproterenol or *in vitro* overexpression of them is associated with increase in liver lipid accumulation and development of hepatic steatosis that may lead to hepatic insulin resistance **(Ghosh et al., 2012; Hurr et al., 2019)**.

2.2 β-Adrenergic receptors and skeletal muscle insulin resistance

The three βAR-subtypes are expressed in skeletal muscle with highest abundance for β2AR **(Williams et al., 1984; Kim et al., 1991)**. Slow-twitch muscles, such as the soleus muscle, have a greater density of βARs than fast-twitch muscles, such as the extensor digitorum longus (EDL) **(Martin 3rd et al., 1989; Ryall et al., 2002; Ryall et al., 2004)**. Notably, the response to β-agonist administration appears to be greater in fast- than in slow-twitch skeletal muscles **(Ryall et al., 2002; Ryall et al., 2006)**. In skeletal muscle, all βARs can couple to either $G\alpha_s$- or $G\alpha_i$-proteins with more predominance for the $G\alpha_s$-subtype **(Xiao et al., 1999; Gosmanov et al., 2002)**. Furthermore, both $G\alpha_i$- and $G_{\beta\gamma}$-proteins can initiate intracellular signaling pathways independent of $G\alpha_s$-proteins **(Glukhova et al., 2018)**.

Noteworthy, $G_{\beta\gamma}$-proteins activation by β-agonists mediates activation of the phosphatidyl inositol 3-kinase (PI3K)/Akt pathway **(Murga et al., 1998; Campbell and Smrcka, 2018)**. As we mentioned previously, Akt activation stimulates both glucose uptake and glycogen synthesis **(Beg et al., 2017)**. Therefore, theoretically activation of the βAR/$G_{\beta\gamma}$/PI3K/Akt pathway by β-agonists should enhance insulin signaling in skeletal muscle.

On the other hand, activation of the AC/cAMP/PKA pathway in skeletal muscle has been found to promote muscle hypertrophy, increase muscle mass, and increase glucose uptake capacity, which may ameliorate systemic insulin resistance **(Chen et al., 2005; Al-Ozairi et al., 2021)**. However, there is a lot of controversy about this role in skeletal muscle. A previous study showed that βARs activation mediates low level of apoptosis in skeletal muscle and this effect is mediated by the β2-subtype not β1 like in cardiac muscles **(Burniston et al., 2005; Burniston et al., 2006)**.

2.3 β-Adrenergic receptors and adipose tissue insulin resistance

Like liver and skeletal muscles, adipose tissue expresses the three subtypes of βARs **(Collins and Surwit 2001)**. All subtypes promote triglycerides hydrolysis and release of free fatty acids (FFAs) in blood stream **(Arner, 1992)**. The underlying mechanisms differ among the βAR-subtypes. β2AR mediates the activation of the $G\alpha_s$-protein/AC/cAMP/PKA pathway, which then mediates the activation of hormone sensitive lipases **(Collins et al., 2004)**. In addition, PKA phosphorylates β2AR impeding further interaction with $G\alpha_s$-protein while promoting its interaction with $G\alpha_i$-protein **(Zamah et al., 2002)**. Then, $G\alpha_i$-protein mediates the activation of the extracellular regulated kinase (ERK), which causes lipid hydrolysis **(Greenberg et al., 2001; Collins et al., 2004)**. On the other hand, β3AR can mediate lipid hydrolysis by concurrent activation of both $G\alpha_s$- and $G\alpha_i$-proteins while β1AR can behave similar to both β2- and β3-AR **(Soeder et al., 1999; Collins, 2012)**.

As mentioned earlier, increased circulating levels of FFAs is highly correlated with systemic insulin resistance through activation of FFA receptors (FFARs) in different types of body tissues, particularly the skeletal muscle. Therefore theoretically, β-agonists can mediate systemic insulin resistance by increasing FFAs circulating levels.

If we consider the findings of previous reports, it seems that β-agonists can mediate systemic insulin resistance by acting on βARs in liver and adipose tissue **(Fig. 1)**. On the contrary, β-agonists enhance insulin signaling and promote glucose uptake by acting on βARs in skeletal muscle. The

question that arises is "Which effect predominates after systemic administration?" To get a plausible answer, we discuss the *in vivo* and *in vitro* actions of β-agonists and antagonists and their effects on systemic insulin resistance.

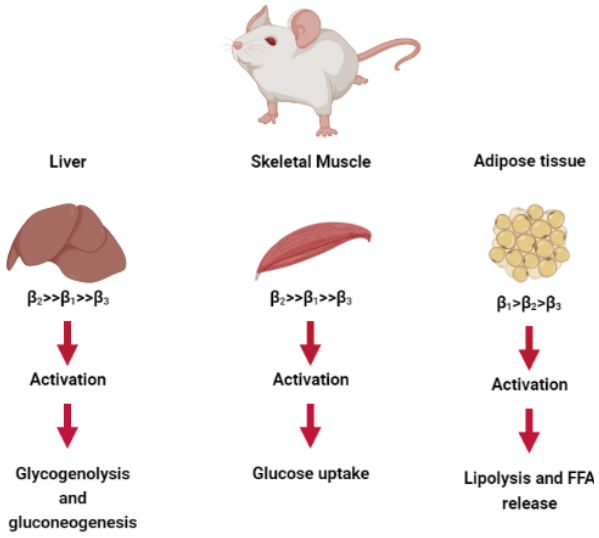
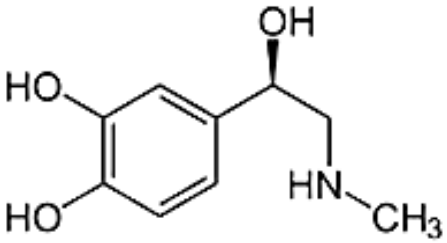


Figure 1: Expression of β-adrenergic receptors in liver, skeletal muscles and adipose tissue and their effects on glucose homeostasis.

3. Ligands of β-adrenergic receptors and their effects on systemic insulin resistance

3.1 Epinephrine

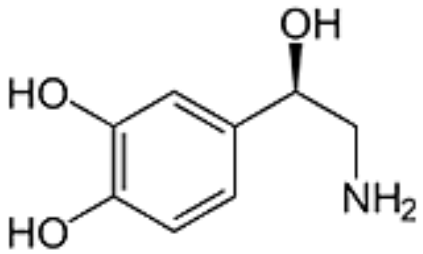


4-[(1R)-1-hydroxy-2-(methylamino) ethyl] benzene-1,2-diol

It is a sympathomimetic catecholamine that can stimulate both α- and β-ARs **(Wong et al., 2012)**. There is a lot of controversy about the metabolic effects of epinephrine, which seems to be highly dependent on the dose and duration of administration in addition to circulating insulin level. Epinephrine, in low dose, has been found to induce hyperglycemia by inhibiting glucose uptake in peripheral tissues and increasing hepatic glucose output. However, in high dose, it induces hyperglycemia by promoting glucagon secretion that inhibits insulin release, reduces glucose uptake, and increases hepatic glucose output **(Gray et al., 1980; Sherwin and Sacca, 1984; Nachar et al., 2011)**. In the same context, epinephrine increases blood glucose levels acutely. However, the chronic effect of epinephrine on blood glucose levels are not clear. A previous study showed that 70-h infusion of epinephrine in combination with other stress hormones elevates blood glucose levels and this effect is highly dependent on epinephrine **(McGuinness et al., 1997)**. On the contrary, another study reported low urine epinephrine levels in patients with metabolic syndrome and that decreased adrenal medullary epinephrine secretion may contribute to the dyslipidemia developed in the insulin resistance syndrome **(Ward et al., 1994)**.

Moreover, it has been found that epinephrine possesses both a stimulatory and inhibitory effect on peripheral glucose uptake. The stimulatory effect was seen on basal glucose uptake and was much smaller than the effect of insulin, however, epinephrine inhibited insulin-mediated glucose uptake by rat hindlimbs and this effect was mediated by βARs as it was totally inhibited by β-blockers such as propranolol, but unaffected by α-blockers such as phentolamine **(Chiasson et al., 1981)**. In the same context, another study demonstrated that epinephrine is capable of inhibiting glucose transport activated by a moderate, but not a high, physiological insulin concentration. In this study epinephrine (24 nM) inhibited glucose transport in the presence of 50 μU/ml insulin in both the epitrochlearis and soleus muscles. However, when muscles were incubated in 100 μU/ml insulin, neither 24 nor 500 nM of epinephrine had significant effects on glucose transport **(Hunt and Ivy, 2002)**.

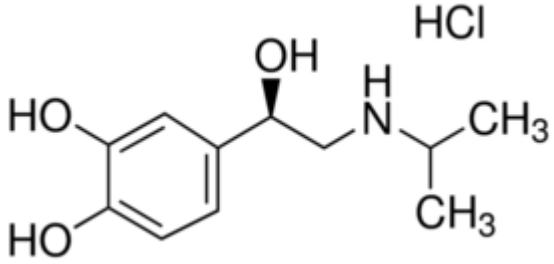
3.2 Norepinephrine



4-[(1R)-2-amino-1-hydroxyethyl] benzene-1,2-diol

It is a sympathomimetic catecholamine that can stimulate αARs more than βARs. In addition, norepinephrine induces less β2AR coupling with $G\alpha_i$ protein than epinephrine **(Wang et al., 2008)**. In contrast to epinephrine, all studies performed on norepinephrine showed acute and chronic systemic insulin desensitizing effects, which may be attributed to the higher activity of norepinephrine on αARs than βARs and the low coupling with $G\alpha_i$ protein **(Marangou et al., 1988; Penesova et al., 2008; Khoury and McGill, 2011)**.

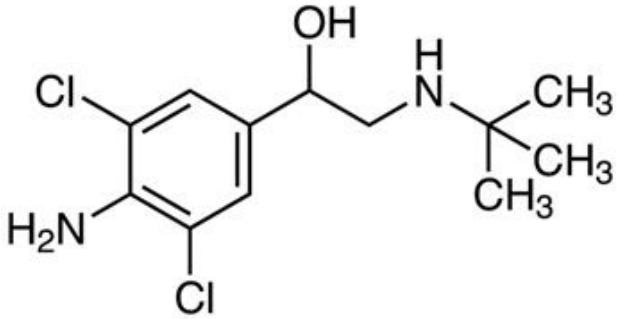
3.3 Isoproterenol



4-[1-Hydroxy-2-(isopropylamino) ethyl]-1,2-benzenediol

Isoproterenol is a synthetic non selective βAR full agonist used as a potent cardiac stimulant **(Zuppa and Barrett 2008)**. Like epinephrine, systemic administration of isoproterenol acutely increases hepatic glucose output and induces insulin resistance **(Hoff and Koh, 2018)**. Unlike epinephrine, the chronic systemic effect of isoproterenol on glucose homeostasis shows a clear increase in systemic insulin sensitivity **(Rousseau-Migneron et al., 1980; Heather et al., 2009; Sato et al., 2014)**. Taking in consideration that isoproterenol activates βARs without affecting αARs and epinephrine activates both types, this may be the first evidence that chronic systemic activation of βARs protects against insulin resistance.

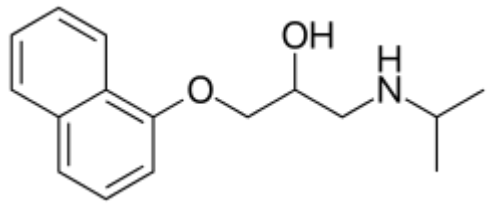
3.4 Clenbuterol



1-(4-Amino-3,5-dichlorophenyl)-2-[(2-methyl-2-propanyl) amino] ethanol

Clenbuterol is a β2-agonist approved in the United States for veterinary use in non-food animals **(Spiller et al., 2013)**. It stimulates β2AR coupling with $G\alpha_i$ protein like epinephrine and more than norepinephrine **(Evans et al., 2013)**. Clenbuterol acutely decreases glucose uptake in skeletal muscle **(Evans et al., 2013; Nagla et al., 2013)**, while chronic systemic administration clearly induces insulin sensitizing effects associated with increased muscle mass, enhanced skeletal muscle glucose uptake, and reduced visceral adiposity **(Pan et al., 2001)**. Interestingly, other selective β2-agonists such as salbutamol, salmeterol, formoterol, and terbutaline showed identical metabolic effects to those of clenbuterol during both acute and chronic administration **(Philipson, 2002)**. This is an additional strong evidence supporting the hypothesis that chronic systemic activation of βARs, especially β2AR, protects against insulin resistance.

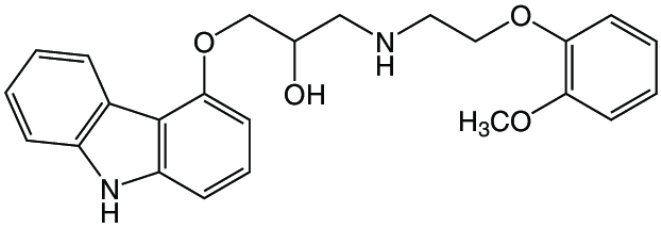
3.5 Propranolol



2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)

Propranolol is a nonselective β-blocker that inhibits the sympathetic effects of catecholamines through βARs **(Routledge and shand, 1979)**. Later, it has been found that propranolol is an inverse agonist to βARs (i.e., it decreases the constitutive activity of these receptors). Moreover, propranolol binds to βARs to activate β-arrestin/ERK pathway **(Luttrell, 2005)**. There is a lot of controversy regarding both the acute and chronic systemic metabolic effects of propranolol. Some studies such as that conducted by **Allison et al., 1969** showed acute systemic insulin sensitizing effects for propranolol probably by inhibiting mobilization of muscle glycogen, lactate-induced hepatic gluconeogenesis, and FFAs release from triglycerides **(Allison et al., 1969)**. Other studies such as that conducted by **Cerasi et al., 1972** showed acute systemic hyperglycemic effects for propranolol mediated by the inhibition of insulin secretion in response to glucose infusion. On the other hand, **Akçay et al., 2005** and **da Silva Franco et al., 2017** showed chronic systemic insulin sensitizing and hypoglycemic effects of propranolol in thermally injured patients and obese mice fed high-fat diet, respectively. The latter effect was probably mediated by blocking β2AR **(da Silva Franco et al., 2017)**. On the contrary, **Groop et al., 1983** showed chronic systemic hyperglycemic effects of propranolol in hypertensive non-diabetic patients after an intravenous glucose tolerance test without affecting insulin secretion.

3.6 Carvedilol

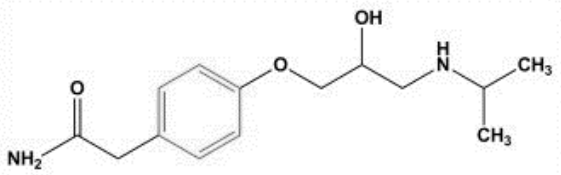


1-(9H-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy) ethyl] amino} propan-2-ol

Carvedilol is a third generation non cardio-selective β-blocker with weak α1 blocking actions **(Mohamed et al., 2019; Ibrahim et al., 2020; Rezk et al., 2021)**. In addition, carvedilol has also been reported to have antioxidant properties **(Abreu et al., 2000; Rolo et al., 2003; Akbas et al., 2005)**. Later, it has been classified as the first member in the β-arrestin biased agonists (**Wisler et al., 2007**). Unlike previous drugs, there are no studies that addressed the acute systemic effects of carvedilol on glucose homeostasis. Therefore, our work group investigated these systemic acute effects in both normal and insulin resistant mice (data under publication). We found that carvedilol did not significantly change glucose tolerance in both normal and insulin-resistant mice after 30 min of intraperitoneal injection. However, carvedilol increased insulin sensitivity in normal mice after 30 min of intraperitoneal injection as assessed by intraperitoneal insulin tolerance test (ITT). Regarding the chronic systemic effects of carvedilol on glucose homeostasis, most studies support the insulin sensitizing effects of carvedilol probably by blocking α1AR and subsequent dilation of blood vessels **(Jacob, 1999; Basat et al., 2006; Ozyıldız et al., 2017)**. Interestingly, our work and another recent research article showed potential role for β-

arrestin2 protein in mediating the insulin sensitizing effects of carvedilol **(Güven et al., 2020; Ibrahim et al., 2020)**.

3.7 Atenolol



2-{4-[2-Hydroxy-3-(propan-2-ylamino) propoxy] phenyl} acetamide

Atenolol is a selective β1AR blocker approved by US Food and Drug Administration (FDA) for the treatment of hypertension, angina pectoris, and acute myocardial infarction **(Wadworth et al., 1991)**. Unlike propranolol and carvedilol, acute systemic administration of atenolol does not prolong hypoglycemia after insulin injection and does not affect glucose homeostasis confirming the potential role of β2AR in mediating these effects of propranolol and carvedilol **(Deacon, 1977; Lyngsøe et al., 1983; Liu et al., 1996)**. On the contrary, chronic systemic administration of atenolol clearly induces insulin resistance that is highly correlated with systemic dyslipidemia **(Pollare et al., 1989; Kuperstein and Sasson, 2000; Reneland et al., 2000; Poirier et al., 2001; Bharati and Singh 2016; Sirenko et al., 2017)**.

Regarding previous discussion, there is a strong evidence that systemic activation of β2ARs causes hyperglycemia and insulin resistance within few minutes to hours while improves glucose homeostasis and insulin sensitivity within few days to weeks. This means that the acute systemic effects of β2-agonists on glucose homeostasis are highly correlated with their effects on hepatic and adipose tissue β2ARs not skeletal muscle receptors. In other words, the contribution of skeletal muscle to systemic glucose homeostasis after systemic administration of β2-agonists is relatively weak compared to liver and adipose tissue. On the other hand, systemic blocking of β2ARs acutely prolongs hypoglycemia after insulin administration while improves glucose homeostasis and insulin sensitivity within few days to weeks. The acute systemic effects of either activation or blocking of β2ARs on glucose homeostasis are reasonable and comprehensible. On the contrary, the chronic effects are obscure and require more clearer interpretation. Therefore, we discuss next the role of $G\alpha_i$-protein/β-arrestin pathway in mediating these effects. We summarized the distinct effects of βARs-ligands on systemic insulin resistance in **Table 1**.

4. $G\alpha_i$/β-arrestin pathway and the metabolic effects of β2-adrenergic receptors

$G\alpha_i$-protein is a subtype of the Gα-proteins family that includes $G\alpha_{i/o}$, $G\alpha_s$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$. $G\alpha_i$-protein inhibits the activity of AC leading to decreased cAMP formation **(De Oliveira et al., 2019)**. Recently, a close interplay between $G\alpha_i$-protein and β-arrestins has been disclosed **(Dwivedi et al., 2018)**. β-arrestins are GPCRs desensitizing proteins, which have been found later to activate G protein-independent signaling **(Jean-Charles et al., 2017)**.

Table 1: Ligands of β-adrenergic receptors and their effects on systemic insulin resistance

Drug	Subject/ Species	Dose/Route/model	Receptor/ mediator	Effect	Reference
Epinephrine	Humans	1.2 μg/m^2/min; infusion; acute	α/β-ARs	Insulin resistance	Sherwin and Sacca, 1984
	Dogs	0.1-0.2 μg/kf/min; infusion; acute	α/β-ARs	Insulin resistance	Gray et al., 1980
	Piglets	0.25-2 μg/kg/min; infusion; acute	α/β-ARs	Insulin resistance	Nachar et al., 2011
	Skeletal muscle	10 nM-0.1 μM; acute	βAR	Insulin resistance	Chiasson et al., 1981
	Skeletal muscle	24 nM; acute	βAR	Insulin sensitization	Hunt and Ivy 2002
	Dogs	0.08 μg/kg/min; infusion; chronic	α/β-ARs	Insulin resistance	McGuinness et al., 1997
Norepinephrine	Humans	25 ng/kg/min; infusion; acute	α/β-ARs	Insulin resistance	Marangou et al., 1988
	Humans	110 ng/kg/min; infusion; acute	α/β-ARs	Insulin resistance	Khoury and McGill, 2011
	3T3-L1 Adipocytes	1μM; acute	βAR	Insulin resistance	Mulder et al., 2005
Isoproterenol	Humans	Drip; acute	βAR	Insulin resistance	Hoff and Koh 2018
	Skeletal muscle	1mg/kg; intraperitoneally; acute	βAR	Insulin sensitization	Sato et al., 2014
	Rats	300 μg/kg/day; subcutaneous; chronic	βAR	Insulin sensitization	Rousseau-Migneron et al., 1980
	Rats	5 mg/kg/day; infusion; chronic	βAR	Insulin sensitization	Heather et al., 2009
	Swiss albino mice	5 mg/kg/day; Intraperitoneally; chronic	βAR	Insulin sensitization	Under publication
Clenbuterol	Skeletal muscle	100 nM; acute	β2AR	Insulin resistance	Nagla et al., 2013
	Skeletal muscle	0.5 mg/kg/day; orally; chronic	β2AR	Insulin sensitization	Hunt et al., 2002
	fa/fa Rats	1mg/kg/day; orally; chronic	β2AR	Insulin sensitization	Pan et al., 2001
	C57Bl/6N mice	0.025 mg/kg/day; Intraperitoneally; chronic	β2AR	Insulin sensitization	Kalinovich et al., 2020
Propranolol	Humans	200 mg/day; orally; acute	βAR	Insulin sensitization	Allison et al., 1969
	Humans	2 mg/kg/day; orally; chronic	βAR	Insulin sensitization	Akçay et al., 2005
	Humans	160 mg/day; orally; chronic	βAR	Insulin resistance	Groop et al., 1983
	C57BL/6J mice	10 mg/kg/day; chronic	β2AR	Insulin sensitization	da Silva Franco et al., 2017
	Swiss albino mice	30 mg/kg/day; Intraperitoneally; chronic	βAR	Insulin sensitization	Under publication
Carvedilol	Humans	50 mg/day; orally; chronic	βAR/α1R	Insulin sensitization	Basat et al., 2006
	Humans	25 mg/day; orally; chronic	βAR/α1R	Insulin sensitization	Ozyıldız et al., 2017
	Rats	10 mg/kg/day; orally; chronic	β-Arrestins	Insulin sensitization	Güven et al., 2020
	Swiss albino mice	10 mg/kg/day; Intraperitoneally; chronic	α1R/βAR/β-Arrestin2	Insulin sensitization	Ibrahim et al., 2020
Atenolol	Humans	5 mg; intravenous; acute	β1AR	Neutral	Lyngsøe et al., 1983
	Humans	100 mg/day; orally; acute	β1AR	Neutral	Deacon 1977
	Skeletal muscle	10 nM-1μM; acute	β1AR	Neutral	Liu et al., 1996
	Humans	50 mg/day; orally; chronic	β1AR	Insulin resistance	Pollare et al., 1989
	Humans	50-100 mg/day; orally; chronic	β1AR	Insulin resistance	Kuperstein and Sasson, 2000
	Humans	50-100 mg/day; orally; chronic	β1AR	Insulin resistance	Reneland et al., 2000
	Humans	50-100 mg/day; orally; chronic	β1AR	Insulin resistance	Poirier et al., 2001
	Humans	25-100 mg/day; orally; chronic	β1AR	Insulin resistance	Bharati and Singh 2016
	Humans	50-100 mg/day; orally; chronic	β1AR	Insulin resistance	Sirenko et al., 2017

This finding led to the discovery of a new class of drugs termed β-arrestin biased agonists **(Ibrahim and Kurose, 2012; Ibrahim et al., 2013; Jean-Charles et al., 2017)**. The first member of this class was carvedilol, which was previously classified as β-blocker **(Jean-Charles et al., 2017)**.

Recently, it has been found that β-arrestin signaling in some conditions may be G-protein dependent, in particular $G\alpha_i$-protein. **Walters et al., 2009** showed that nicotinic acid-mediated activation of ERK is dependent on both $G\alpha_i$-protein and β-arrestin1 **(Walters et al., 2009)**. In the same context, **Wang et al., 2018** showed that mechano-activation of the angiotensin II type 1 receptor induced β-arrestin biased signaling through $G\alpha_i$-coupling **(Wang et al., 2018)**. Moreover, **Wang et al., 2017** showed that $G\alpha_i$ is required for carvedilol-induced β1AR β-arrestin biased signaling **(Wang et al., 2017)**. β2-Agonists acutely mediate hyperglycemia and insulin resistance by the activation of β2AR/$G\alpha_s$/AC/cAMP/PKA pathway in the liver leading to hepatic glycogenolysis and gluconeogenesis and lipid hydrolysis with subsequent elevation of circulating FFAs in adipose tissue **(Fig.2)**. However, persistent activation of β2AR shifts the coupling towards $G\alpha_i$-protein instead of $G\alpha_s$-subtype. Therefore, during chronic systemic administration of β2-agonists the predominant pathway is the $G\alpha_i$-rather than $G\alpha_s$-protein dependent signaling pathway. Probably, this shift toward $G\alpha_i$-protein pathway may be associated with the activation of β-arrestin signaling, which improves glucose homeostasis and insulin sensitivity as mentioned earlier **(Fig. 2)**. Supporting this assumption, a recent study showed that the clenbuterol-induced skeletal muscle hypertrophy is both $G\alpha_i$/β-arrestin1 dependent (**Kim et al., 2018**). Although another recent study showed that clenbuterol-induced systemic glucose uptake is independent of the β-arrestin1/2 activity in the skeletal muscle (**Meister et al., 2019**), the role of $G\alpha_i$/β-arrestin pathway in liver and adipose tissue was not previously examined. Taking in consideration that the role of liver and adipose tissue is more prominent than that of skeletal muscle in mediating β2-agonists systemic effects as we previously mentioned, it will be interesting to investigate the role of $G\alpha_i$/β-arrestin pathway in these tissues.

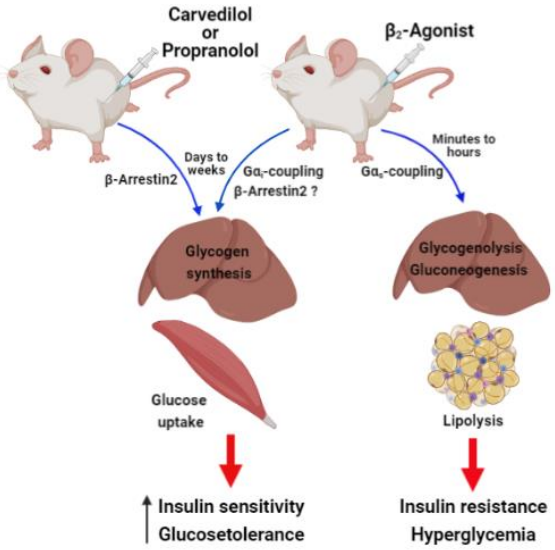


Figure 2: Acute and chronic effects of β-adrenergic receptor agonists and antagonists on glucose homeostasis: Role of $G\alpha_{s/i}$-proteins and β-arrestin2.

On the other hand, β-blockers such as propranolol have been found to acutely prolong hypoglycemia after insulin administration by blocking β2ARs leading to inhibition of hepatic glucose output and release of FFAs into the circulation. In the same context, propranolol has been found to activate β-arrestin signaling, which can mediate insulin sensitizing effects. Because, β-arrestin signaling is long lasting compared to G-protein

signaling, the chronic effects of propranolol are more likely to be mediated by the former one. Interestingly, our work revealed a link between the chronic insulin sensitizing effects of propranolol and hepatic β-arrestin2 signaling (data under publication) **(Fig. 2)**. Similarly, carvedilol acute and chronic metabolic effects can be interpreted in the same way. Also, our work and another research group showed potential role for β-arrestin2 signaling in mediating the metabolic effects of carvedilol.

5. Conclusion and future perspectives

β-Adrenergic receptors can both induce and ameliorate insulin resistance depending on the β-adrenergic receptor subtype, the duration of stimulation and the type of affected tissue. Systemic use of β2-agonists acutely mediates insulin resistance while improves it on long-term use. These opposing effects may be attributed to the shift from $G\alpha_s$-coupling in short-term use to $G\alpha_i$-coupling in long-term. Furthermore, $G\alpha_i$-coupling may mediate the insulin sensitizing effects by the activation of β-arrestin signaling especially in liver and adipose tissue. However, further future studies are required to confirm this assumption. On the other hand, the ability of certain types of β-blockers such as carvedilol and propranolol to chronically reduce systemic insulin resistance may be mediated by the activation of β-arrestin signaling .

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الملخص العربي:

دور مستقبلات بيتا الأدرينالية في مقاومة الأنسولين: تحفيز ام منع ؟

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مستقبلات بيتا الأدرينالية ، خاصة النوع الفرعي 2 ، هي منظم رئيسي لتوازن الجلوكوز. أظهرت الدراسات السابقة أن تنشيط مستقبلات بيتا الأدرينالية في الأنسجة الكبدية والدهنية يعمل على فقدان الحساسية لتأثيرات الإنسولين. على العكس من ذلك ، فإن تنشيطها في العضلات الهيكلية يعزز امتصاص الجلوكوز. ومع ذلك ، هناك الكثير من الجدل فيما يتعلق بالتأثيرات الأيضية لمحفزات بيتا الأدرينالية أو مثبطاتها. لقد ثبت أن نواهض البيتا-2 تضعف إلى حد كبير توازن الجلوكوز في حين انها تحسنه من خلال الإستخدام طويل المدى. في نفس السياق ، وجد أن الاستخدام قصير و طويل المدى لأنواع معينة من مثبطات بيتا يعزز عمل الأنسولين. في هذه المقالة المرجعية ، نحاول توضيح الآليات الأساسية التي تنظم التمثيل الغذائي للجلوكوز بعد الاستخدام القصير و الطويل المدى لمحفزات ومثبطات مستقبلات بيتا الأدرينالية في محاولة للإجابة على السؤال "هل تحفز مستقبلات بيتا الأدرينالية أم تمنع مقاومة الأنسولين؟"