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β-Blockers in Metabolic and Endocrine Perspectives

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ABSTRACT

Catecholamine, through α-adrenergic receptor and β-adrenergic receptor activation, plays many roles in body's physiological and pathophysiological processes. β-adrenergic receptor has different effect pursuant to receptor type, receptor location and G protein activation in the receptor. Beta receptor blockers (β-blockers) are a drug commonly used for cardiovascular disease. There are 3 different generations of β-blockers. In addition to their great advantages in cardiovascular, β-blockers also have metabolic and endocrine effects. β-blocker may influence sugar and insulin, fat, melatonin, cancer, blood uric acid and thyroid hormone metabolism. These metabolic effects may be disadvantageous, which mostly takes place with initial generation β-blockers. Third generation β-blockers do not show disadvantageous metabolic effect. However, early generation β-blockers may be advantageous in certain condition.

INTISARI

Katekolamin,melalui aktivasi reseptor α-adrenergik dan reseptor β-adrenergik memiliki banyak peran dalam proses fisiologi dan patofisiologi tubuh. Reseptor β- adrenergik memiliki efek yang berbeda sesuai dengan jenis reseptor, letak reseptor, serta aktifasi protein G pada reseptor tersebut. Penghambat reseptor beta (β- blocker) merupakan salah satu obat yang banyak digunakan dalam bidang penyakit kardiovaskular. Saat ini terdapat 3 generasi β- blocker yang berbeda. Selain manfaat besarnya di bidang kardiovaskular, β- blocker juga memiliki efek di bidang metabolik dan endokrin. β- blocker dapat mempengaruhi metabolisme gula dan insulin, lemak, melatonin, kanker, asam urat darah, dan hormon tiroid. Efek metabolik ini bisa menjadi efek yang merugikan. Efek metabolik merugikan ini sebagian besar terdapat pada β- blocker generasi awal. β- blocker generasi ke 3 tidak menunjukkan efek metabolik yang merugikan. Namun, β- blocker generasi awal mungkin lebih bermanfaat pada keadaan tertentu.

Introduction

The β-blockers are commonly used in cardiovascular disease. The European Society Of Cardiology and American Heart Association includes β-blockers into level of evidence 1 in the disease management of chronic heart failure, cardiac arrhythmia, and stable coronary artery disease.[1,2,3,4] In addition to their great advantages in the cardiovascular system, β-blockers also have metabolic and endocrine effects. Through adrenergic alpha and beta receptors, catecholamine plays many roles in body's physiological metabolic processes.[5] This article will specifically discuss the effects of β-blockers in metabolic and endocrine perspectives, including glucose metabolism, fat metabolism, melatonin metabolism, bone metabolism, cancer metabolism, uric acid metabolism, and thyroid hormone metabolism.

B-Blockers Action Mechanism and Classification

Catecholamine rules many body's physiological and pathophysiological processes. Catecholamine has some receptors, i.e α-adrenoceptor, β-adrenoceptor and dopamine receptor. Adrenoceptor antagonist drug is a drug related to adrenergic receptor but does not result in metabolic effects (hereinafter referred to as α-blocker and β-blocker). This drug may inhibit the activities of α-adrenergic receptors (α-1 and α-2) and β-adrenergic receptors (β-1, β-2, β-3). α-1 receptor is located in

postsynaptic effector cell of smooth muscle and α-2 receptor is located in presynaptic nerve terminal of smooth muscle. β-1 receptor is located in postsynaptic effector cell, particularly in heart, brain, lipocyte and juxtaglomerular apparatus. β-2 receptor is located in postsynaptic effector cell of smooth muscle and cardiac muscle. β-3 receptor is located in postsynaptic effector cell, particularly in fat cell and heart.[5]

Each of β-adrenergic receptors has different effect pursuant to receptor type, receptor location and G protein activation. β1-adrenergic receptor is paired with G stimulant (Gs) protein. β2-adrenergic receptor is paired with G stimulant (Gs) protein and G inhibitor (Gi) protein (Gs protein is more dominant in β2 receptor). β3-adrenergic receptor is paired with Gi protein and Gs protein.[6] The bond between receptor and protein will stimulate adenylyl cyclase and improve cAMP of cell and activation of protein kinase A (PKA).[5] This process is followed with phosphorylation of L-type calcium channel and calcium release channel from sarcoplasmic reticulum. This response increases intracellular calcium concentration and triggers contraction in appropriate effector cells.[7]

β-blocker may be classified into 3 generations. First generation β-blockers are non-selective β-blockers which inhibit β-1 and β-2 receptors, for example, propranolol and sotalol. Second generation β-blockers are often called cardioselective β-blockers since they have higher affinity to inhibit β-1 receptor existing in heart organ, for example, bisoprolol and metoprolol. Third generation β-blockers are β-blockers with vasodilation effect, for example, carvedilol and nebivolol.[6] By vasodilation effect capability, β-blockers are divided into 2, namely non-vasodilating β-blockers and vasodilating β-blockers. First and second generation β-blockers are generally included in early generation (non-vasodilating) β-blockers, while third generation β-blockers are included in vasodilating β-blockers.[10]

B-Blockers and Glucose Metabolism

Administering non-vasodilating β-blocker to a patient with cardiovascular disease has negative effect on glucose metabolism and reduces insulin sensitivity. These are clearly disadvantageous for diabetes patient with cardiovascular disease.[11] For non-diabetic patient administered with β-blocker, the concept of impaired insulin sensitivity will not increase blood glucose level, but pancreatic β-cell will compensate it by producing more insulin (hyperinsulinemia). At certain period of time, pancreatic β-cell will be exhausted and cannot compensate it by forming insulin, thus new onset type 2 diabetes mellitus occurs.[12]

Although the exact mechanism is not clear, this is related to hemodynamic effects of β-blockers.[11] Non-vasodilating β-blockers will conversely improve α-1 adrenergic activity (it cause vasoconstriction), reduce blood flow to muscle, and reduce glucose uptake stimulated by insulin in peripheral organs. Non-vasodilating β-blockers also disturb first phase of insulin secretion from pancreatic β-cells.[12] Metoprolol and atenolol reduce insulin sensitivity as marked with reduction of glucose uptake in cells.[13] Increasing body weight may also occur with patient with non-vasodilating β-blocker therapy. This shows correlation between β-blockers utilization and risk of developing diabetes.[12]

A contradictory result is obtained with vasodilating β-blocker administration. This drug may improve glucose control parameter and insulin sensitivity. The mechanism on which this metabolism profile improvement is based is that vasodilating β-blocker drug prevents norephinephrine bond with α-1 adrenergic receptor. This causes blood vessel vasodilation, increases blood flow to muscle and improve glucose uptake.[11] Nebivolol shows advantageous effect in insulin sensitivity and fat metabolism, because of the capability of nebivolol vasodilation mediated with nitric oxide effect and anti-oxidative effect.[14] Carvedilol also has equal effect to that of nebivolol in controlling glucose parameter, insulin resistance and fat profile.[15]

β-blockers must be administered more cautiously to patient with glucose metabolism disorder. Besides increasing glucose level and insulin resistance, β-blockers also has risk of developing prolonged and refractory hypoglycemia. In case of hypoglycemia, body will show physiological responses in order to increase glucose, one of which is to increase epinephrine secretion from adrenal medulla. Ephineprine will stimulate glucagon secretion from pancreatic alpha cell and stimulate gluconeogenesis and hepatic glycogenolysis.[16] Non-selective β-blocker administration will inhibit this physiological mechanism, and cause prolonged hypoglycemia.[17] β-blockers may also weaken neurogenic and neuroglycopenic symptoms in hypoglycemia, which thus develops a dangerous condition of unconscious hypoglycemia.[18]

B-Blockers and Fat Metabolism

β-3 adrenoreceptor plays role in regulating lipolysis. β-3 adrenoreceptor stimulation may stimulate fat oxidation and increase energy expenditure. Therefore, β-3 adrenoreceptor stimulation may reduce total body fat, maintain lean body mass and improve insulin sensitivity.[19]

Catecholamine, adrenaline and noradrenaline have different lipolysis effects based on their bond with sub-type of adrenergic receptor located on the surface of adipocyte plasma membrane. During adrenergic receptor activation, G protein sub-unit is released to activate or inhibit adenylylcyclase (AC). This activity depends on the sub-type of G protein. Activated AC improves cAMP level at cytoplasm, which will activate protein kinase A (PKA). PKA will phosphorylate hormone-sensitive lipase (HSL) and stimulate lipolysis.[20,21]

Monotherapy using first and second generation β-blockers may increase triglyceride level in the blood and reduce HDL level in the blood.[22] Atenolol increases glucose level and fat profile of patient with essential hypertension.[23] Another study shows that β-blocker administration to chronic heart failure patient may increase total body fat mass.[24] This basic mechanism is caused by blocking of catecholamine, which plays important role in lipolysis.[20]

Nebivolol is a racemic mixture consisting of D-nebivolol (+SRRR nebivolol) and L-nebivolol (–RSSS nebivolol). Nebivolol is different from other β-blockers which structurally has the same symmetric configuration.[25] D-nebivolol primarily serves as selective β-1 blocker, while L-enantiomer serves as β-3 adrenergic receptor agonist. Nebivolol stimulates lipolysis and stimulates thermogenic through β-3 adrenergic receptor stimulation. Nebivolol reduces total fat droplet cells in the body.[26] Nebivolol becomes an option of therapy to treat hypertension patient with fat metabolism and glucose disorders.[14] Carvedilol and nebivolol have the same advantageous effects in terms of fat metabolism parameter.[15]

B-Blockers and Melatonin Metabolism

Melatonin is a product of serotonin found in pineal gland. Melatonin is secreted at night and plays an important role in human sleeping pattern and circadian rhythm. Melatonin has melatonergic 1 and melatonergic 2 (MT1 and MT2) membrane receptors located in cardiovascular system (cardiomycocytes, left ventricle, and coronary artery).[27] MT1 receptor causes arterial vasoconstriction, inhibits cancer cell proliferation, and modulates reproduction and metabolic systems. Meanwhile, MT2 activation will cause vasodilating effect, improve body immune system and inhibit dopamine release.[28]

Exogenous melatonin administration serves to reduce nocturnal hypertension, improve systolic and diastolic blood pressure, reduce pulsation index at internal carotid artery, reduce platelet aggregation and reduce blood catecholamine level. Blood melatonin declining level is related to essential hypertension, coronary artery disease and chronic heart failure.[29] β-adrenergic receptor activation in pineal gland is the main pathway of melatonin synthesis. This β- receptor activation stimulates melatonin formation through activation of cyclic AMP and protein kinase a (PKA) and activates translocation of NF-kb. Propranolol inhibits melanocyte formation by blocking β-adrenergic receptor activation.[30] Melatonin synthesis inhibition will reduce blood melatonin level, which cause sleep disorder with patient administered with propranolol.[31] Propranolol and atenolol evidently reduce melatonin production at night. However, not all β-blockers reduce blood melatonin. Carvedilol and nebivolol do not evidently reduce melatonin production.[32,33]

B-Blockers and Cancer Metabolism

The previous research showing the role of β-adrenergic receptor in cancer metabolism is conducted by Schuller and Cole. Their study shows significant increase in proliferation of human lung adenocarcinoma cells in response to β-receptor agonist isoproterenol administration.[34] Three sub-types of b-adrenergic receptors (β-1, β-2, and β-3 receptors) exist in the tissue of primary tumor and metastatic tumor, such as brain, lung, liver, kidney, adrenal gland, breast, ovary, prostate, lymphoid tissue, bone marrow and blood vessel. β-adrenergic receptor activation regulates cell function related to cancer growth, including epithelial cells, blood vessel myocytes and pericytes, adipocyte, fibroblast, neuron and glia.[35]

Stress may induce catecholamine, which plays a role in the metastasis process of cancer cell tissue. Sympathetic nervous system activation by catecholamine may influence various molecular pathways connected to cancer cells. This process directly regulates β-adrenergic receptor existing in tumor cell microenvironment, such as macrophages and small blood vessels.[35,36] β-3 adrenergic receptor is one of the main receptors involved in SIRT1, p53, mTOR and microRNA-16 signaling pathways regulation which plays a role in cancer growth.[37] Noradrenaline stress hormone improves melanoma cancer microenvironment through β-3 adrenoreceptor and β-2 adrenoreceptor activations. These activations increase recruitment of cancer fibroblasts, M2 macrophages. This process will maintain pro-inflammatory and pro-angiogenic environments needed for proliferation and cancer cell metastasis.[38] β-adrenergic signal activation increase infiltration of macrophage $CD11b^{+}$ F4 / 80^{+} into primary tumor parenchyma. This process increases prometastatic gene expression. β-blocker (propranolol) administration may inhibit macrophage infiltration induced by stress hormone (catecholamine) and inhibit tumor from spreading into body tissues.[39] β-blocker administration may become future therapy to reduce the mortality rate of cancer patients.[40]

Carvedilol inhibits epidermal growth factor (EGF) of $JB6p^{+}$ cells (non-cancer skin cell model which may transform to be malignant upon exposure to tumor promoters) which experiences malignant transformation. Carvedilol also inhibits the activation of protein activator-1 (AP-1) mediated by EGF. This shows that carvedilol has chemopreventive activity against skin cancer.[41] Non-selective β-blocker effectively inhibits melanoma progress.[42] Propranolol inhibits melanoma by reducing tumor angiogenesis regulation and tumor melanoma cell proliferation. Propranolol evidently increases prognosis of melanoma patient significantly.[43] β-blocker administration (propranolol) may reduce breast cancer progress and death rate.[34,44] Propranolol also reduces metastasis risk, recurrence risk and breast cancer death rate.[45] Metoprolol, bisoprolol, carvedilol and atenolol may reduce risk of developing colorectal cancer.[46]

B-Blockers and Bone Metabolism

Sympathetic nervous system is one important regulator of bone metabolism (particularly bone resorption). β-adrenergic activation increases production of bone-active cytokines such as interleukin-6, interleukin-11 and prostaglandin E2.[47] Increased sympathetic activity mediated by catecholamine in osteoblast β-adrenergic receptor will reduce osteoblast proliferation and differentiation.[48] β-adrenergic stimulation also increases osteoclast differentiation factor (ODF) expression in osteoblastic cells. ODF stimulates formation of osteoklast for bone resorption.[49] Therefore, β-blocker administration may increase bone formation and strength, as well as reduce risk of bone fracture.[50]

In hypertensive patient administered with β-blocker therapy, there is an increase of bone mineral density in femoral neck and lumbar spine. β-blocker users have lower

risk of bone fracture than they who do not use β-blockers.[50,51] Large meta-analysis research with 907,000 subjects shows that β-blockers do not significantly reduce risk of bone fracture of old people.[52]

B-Blockers and Uric Acid Metabolism

Low filtration function of renal glomerulus is one of important risk factors of increased blood uric acid level. A decrease of estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m2 is the threshold of increased blood uric acid level.[53] Non-selective β-blockers may activate α-receptor in peripheral blood vessels which causes blood vessel vasoconstriction. Therefore, β-blockers induce renal vasoconstriction and reduce renal filtration rate.[12] In patients who use β-blocker, there is negative correlation between eGFR and serum uric acid level. B-blockers may increase blood uric acid level through eGFR reduction mechanism.[54] Hypertensive patients who use β-blockers are at relative risk 1.4 times higher to develop gout hyperuricemia.[55] However, hypertensive patients who use vasodilating β-blocker (carvedilol) do not show increased blood uric acid level effect.[56]

B-Blockers and Thyroid Hormone Metabolism

Sympathoadrenal system and thyroid hormone have mutually strengthening interaction. Catecholamine may stimulate conversion of T4 to T3. T3 activity is 10 times higher than T4. There are 2 conversion pathways of T4 to T3, which are type I (D1) and type II (D2) deiodinase. The two pathways are related to iodothyronine 50-deiodinase activity. Pathways type I (D1) exists in liver, kidney, and thyroid gland. Pathway D1 is the main source of T3 plasma through extrathyroid production. β-adrenergic blocker may actively inhibit conversion of T4 to T3.[57] Inactive D-propranolol isomer and active L-propranolol isomer equally strongly inhibit iodothyronine 50-deiodinase activity. β-blocker's inhibiting potential is correlated with fat solubility and cell membrane stabilizing ability.[58] Propranolol reduces plasma T3 level and increases reverse plasma T3 level (metabolite form of inactive thyroid hormone).[59] Propranolol may cause euthyroid hyperthyroxinemia.[60]

Table 1 summarizes the role of beta blocker receptors on hormones and the body's metabolism. The opposite effect appears when the receptor is inhibited by using a beta blocker.

Table 1.
β -adrenergic receptor responses in endocrine and metabolic perspectives

	β- 1	β- 2	β- 3
G Protein Activation	Gs	Gi and Gs	Gi and Gs
Result of ligand binding	Stimulation of adenylyl cyclase, increased camp	Stimulation of adenylyl cyclase, increased camp	Stimulation of adenylyl cyclase, increased camp
Location	Postsynaptic effector cells	Postsynaptic effector cells	Postsynaptic effector cells
Adipocytes			Lipolysis and thermogenesis
Liver		Glycogenolysis and Gluconeogenesi	
Vascular smooth muscle		Relaxation Peripheral glucose uptake Insulin sensitivity	
Melatonin secretion	Increase melatonin secretion	Increase melatonin secretion	
Bone metabolism	Osteoclast differentiation	Increase osteoblast activity	
Cancer metabolism	Tumorigenesis Angiogenesis Cell Proliferation Tumor Micro environtment	Tumorigenesis Angiogenesis Cell Proliferation Tumor Micro environtment	Tumorigenesis Angiogenesis Cell Proliferation Tumor Micro environtment
Kidney and Uric acid metabolism Thyroid metabolism	Secretion of renin Increase renal blood flow	Increase renal blood flow Uric acid excretion Stimulate T4 to T3 convertion	

Conclusion

Sympathetic nervous system has many effects on body metabolisms. Inhibiting sympathetic system using β-blocker may influence other body metabolisms, of which effects may be unwanted. Third generation β-blockers (vasodilating β-blockers) do not show adverse metabolic effects. Early generation β-blockers (non-vasodilating β-blockers) may be more advantageous in certain condition, even if they have adverse metabolic effects.

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