Genomics and Applied Biology 2018, Vol.9, No.1, 1-5
http://gab.biopublisher.ca

Research Report Open Access

Research Progress of Marinobufagenin and Salt-Sensitive Hypertension

Xiaoxiao Fang, Xinghui Jing, Junfeng Wang, Yuan Gao
Zunyi Medical College in Zhuhai campus, Zhuhai, China, 519000
Corresponding author email: 705888097@qq.com

Genomics and Applied Biology, 2018, Vol.9, No.1 doi: 10.5376/gab.2018.09.0001
Received: 15 Nov., 2017
Accepted: 05 Dec., 2017
Published: 12 Jan., 2018

Preferred citation for this article:
Fang X.X., Jing X.H., Wang J.F., and Gao Y., 2018, Research progress of marinobufagenin and salt-sensitive hypertension, Genomics and Applied Biology, 9(1): 1-5 (doi: 10.5376/gab.2018.09.0001)

Abstract Salt-sensitive hypertension is a special type of hypertension. Because of its special pathogenesis and clinical features, it has attracted more and more attention in recent years. Marinobufagenin is a kind of endogenous digitals-like substance, which is the unitary ligand of Na^+/K^+ ATPase widely distributed in human and animal. Marinobufagenin mediates water sodium retention, increases blood pressure, and interferes myocardial and vascular fibrosis and other pathologic mechanisms by blocking Na^+/K^+ ATPase and various signaling pathways, which playes an importent role in the occurrence and development of salt-sensitive hypertension. This article hlights recent advances of the relation between marinobufagenin and salt-sensitive hypertension.

Keywords Marinobufagenin; Salt-sensitive hypertension; Na^+/K^+-ATPase; Endogenous digitals-like substance

1 Salt-Sensitive Hypertension

Salt is one of the crucial risk factors of essential hypertension. A mass of clinical observations, animal experiments and ecological studies have documented the intimate association between salt and blood pressure. The different blood pressure response of individuals to salt load showed a discrete distribution, which confirmed the presence of salt sensitivity. Salt sensitivity is the genetic basis of salt connects hypertension, is an intermediate genetic phenotype of essential hypertension. The salt sensitivity of blood pressure, defined as an exaggerated pressor response to dietary salt intake, jointly determined by genetic factors, age, body mass index (BMI), concomitant diseases, ethnic factor, increases the risk of hypertension (Carey et al., 2012; Kotchen et al., 2013; Felder et al., 2013; Frame et al., 2017), and the associated hypertension defined as salt sensitivity hypertension (salt-sensitive hypertension, SSH). Some people have significant blood pressure increase after high salt intake is called salt-sensitive subjects, while the other group have no obvious increase in blood pressure is called non-salt-sensitive subjects. SSH is an important characteristic of hypertension in China, affects approximately 50% of hypertensive patients, 25% of normotensive adults (Kotchen et al., 2013; Felder et al., 2013) and about 40% of the teenages have salt sensitivity in positive family history of hypertension (Mou et al, 2012). It is a complex disease related to regional, ethnic, demographic and social factors, as well as an independent risk factor for cardiovascular disease.

2 Endogenous Digitals-like Substance and Marinobufagenin

Endogenous digitals-like substance (ELDS)， which has similar characters with exogenous digitalis in structure, physico and chemical properties and biological functionis, is classified into two groups. Endogenous cardenolids have similar structure with digitalatis from plant, including endogenous ouabain (EO) and endogenous digoxin. Another group is endogenous bufadienolides, including endogenous marinobufagenin (MBG), telocinobufagin and bufalin，which have similar structure with bufotoxin that originally discovered in skin of amphibians (Schoner et al., 2007; Wang et al., 2011). Significantly, MBG has intimate association with salt sensitive hypertension and involves multiple pathogenesis.

3 Marinobufagenin and Salt Sensitive Hypertension

3.1 Level of marinobufagenin in salt sensitive hypertension

MBG is mainly produced in the hypothalamus and adrenal cortex. Some animal experiments studied ELDS in

Dahl rat discovered MBG had inseparable relation with EO compared level of EO and MBG in central and peripheral found them have same model. Transient responses of endogenous ouabain preceded the persistent elevation of MBG excretion in acute and chronic NaCl-loaded DS rats (Fedorova et al., 2000; 2005; 2007).

In the acute NaCl-loaded experiment, transientpeak responses of endogenous ouabain in the amygdale, hippocampus preceded stimulation of endogenous ouabain in the hypothalamus and pituitary，whereafter，level of MBG excretion elevated persistently. This model suggested persistent elevation of MBG excretion may stumilated by EO sharp increase in brain. Consistented with the hypothesis, the pretreatment of NaCl-loaded rats with the anti-MBG antibody prevented BP elevation, reduced renal sodium excretion and restored the activity of the sodium pump in the proximal convoluted tubules (Fedorova et al., 2007). Subsequently, Olga V et al. implemented acute salt-load to Dahl rats, the level of EO transient rised in hypophysis cerebri, plasma and kidney while the level of renal MBG excretion and plasma MBG elevated persistently, the level of Ang Ⅱ in hypophysis cerebri and adrenal cortex also increased. These consequences caused renal sodium pump activity reducing, sodium excretion increasing and blood pressure elevation, which could be alleviated by anti-MBG antibody. Anti-EO antibody could reduce elevation of Ang Ⅱ in hypophysis, losartan had similar fountion with anti-EO antibody, but didn't impact EO release. So different from the previous consequences that Ang Ⅱ secreted a variety of steroid, including EO, via AT2 receptors pathway, the experiments revealed adrenal cortical cells secreted MBG via AT1 receptor pathway as this approach can be inhibited by Losartan (Fedorova et al., 2005). Fedorova et al. had new progress in synthesized of MBG They found MBG producted in placenta and adrenal cortex via a 'acidic' bile acid pathway outside the liver like amphibian. Steroids are derived from cholesterol through the traditional steroidogenesis pathway initiated by enzyme CYP11A1, and via the acidic bile acid pathway make it become bufadienolide, which is controlled by enzyme CYP27A1 (Fedorova et al., 2015). The mechanism of marinobufagenin biosynthesis in mammals, however, remains unknown. But These findings will help to understand the role of marinobufagenin in highly prevalent human cardiovascular diseases.

3.2 Marinobufagenin and sodium excretion

The bioactive steroid, marinobufagenin, is a specific ligand of Na^+,K^+-ATPase (NKA), which can inhibit the founction of NKA. MBG is initially defined as the "natriuretic hormone" suggests that its sodium excretion was the most important founction be attented. Previous studies have shown that MBG was positively correlated with urinary sodium excretion. In the early stages of the long-term salt load, MBG reactively increased blood pressure to raise sodium excretion as response to sodium elevation in body. In the case of long-term sodium salt load, the natriuretic effect of MBG was difficult to compensate, but the amount of excretion continues to rise, and the excretion of MBG is gradually increasing. The level of renal MBG and urinary MBG decreased, but the plasma MBG did not.

Dietary sodium restriction reduced urinary marinobufagenin excretion and that might relieve systolic BP and aortic stiffness (aortic pulse-wave velocity) by reducing oxidative stress (Jablonski et al., 2013). Endogenous marinobufagenin increased for self-adaption in salt sensitive hypertension, which reduced proximal tubular sodium reabsorption and promoted sodium excretion through inhibiting Na^+,K^+-ATPase α_1. This mechanism resulted in sustained stimulates biosynthesis and overproduction of MBG while sodium excretion is sufficient. Overproduction of MBG inhibited Na^+,K^+-ATPase α_1 and enhanced vasoconstriction which leaded to prehypertension. 24 hours urinary sodium excretion were not significantly different in salt-sensitive subjects and non-salt-sensitive subjects, but the nocturnal urine sodium excretion of non-salt-sensitive people was significantly lower than that of salt sensitive and the percentage of nocturnal urinary sodium in total is also significantly higher than that of non-salt sensitive people (Mou et al., 2014). The main reason is that the salt sensitive person's kidneys have a natriuretic deficiency, which causes the sodium peak to be delayed after high salt intake, and the sodium excretion capacity decreases, resulting in remaining sodium retention. Body reconstructs stress urinary natriuretic function to extrect the sodium retention in the body and increase nocturnal sodium excretion passively, then compensatory elevated blood pressure at night and showed Non-dipper change.

3.3 Marinobufagenin and blood pressure

Many researches indicated that MBG was closely related to blood pressure (Anderson et al., 2008). It was thought that EO has a more important role in blood pressure regulation, but subsequent research has found the lower concentration of MBG can cause vasoconstriction relative to uabain in blood vessels of individuals. Blood pressure reduced in the pretreatment of hypertension model rats with the anti-MBG antibody but not in rats with anti-EO antibody. Therefore in this genetic form of salt sensitive hypertensive rats, the increase of MBG level was related to the formation of hypertension (Fedorova et al., 2000). Summarized from previous experimental results, MBG regulated blood pressure from two mechanisms. On the one hand, MBG was combined with NKA on vascular smooth muscle to reduce the transport of sodium ions, caused Intracellular Ca^{2+} increases, exacerbated the constriction of blood vessels. On the other hand, MBG combined with the NKA of the renal tubular cell membrane to reduce the reabsorption of filtered sodium and to increase sodium retention. Recent studies found that the relation of plasma MBG and urinary MBG excretion between systolic and diastolic blood pressure are different, and the effect of MBG on blood pressure was related to gender.

Olga et al. found that plasma MBG was related to 24h dynamic systolic and diastolic pressure while urinary MBG excretion just related to 24h dynamic diastolic pressure (Fedorova et al., 2015). Gender analysis of salt sensitive hypertension patients showed that significant correlation of MBG and BP just existed in male, which might because progestational hormone have founction of excreting sodium and competing with CTS for sodium pumps (Morrill et al., 2008). Be same as the MBG responses of Dahl rats, subjects with MBG increased have significant elevation in systolic and diastolic pressure after salt-load, suggesting that MBG was an important intermediary for blood pressure elevation induced by salt in male. According to relevant clinical literature of blood pressure monitoring in salt sensitive hypertension patients found their nocturnal blood pressure was not reduced significantly, the nocturnal blood pressure trough is not clear or even disappear and presented Non-dipper (the morning peak of blood pressure and not enough decrease in nocturnal blood pressure), and dietary sodium restriction or diuretic could reduce blood pressure change induced by salt. This process might be one of the important mechanisms of target organ damage in such patients, and suggested the association between non-dipper of hypertension patients with salt sensitivity (Yoshinaga et al., 2012; Mou et al., 2014; Xu, 2015).

3.4 Marinobufagenin and fibrosis

Marinobufagenin binding to Na^+,K^+-ATPase initiates profibrotic cell signaling, and heightened marinobufagenin levels are implicated in the pathogenesis of hypertension, preeclampsia, and chronic kidney disease. Recent studies on MBG have gradually tended to it's founction in fibrosis. MBG contributes to fibrosis of myocardial and arterial and aortosclerosis. Dietary sodium restriction relieves even reverses these pathologic damage is the best proof. Jablonski et al. (2013) found that dietary sodium restriction performed in middle-aged/older adults with moderately elevated systolic BP would reduce urinary marinobufagenin excretion as well as systolic BP and aortic pulsewave velocity and relieve aortosclerosis. NKA participated in signal and not activated sodium pump through Src and Epidermal Growth Factor Receptor (EGFR) resided on fossa (Liang et al., 2007). Study found that MBG increased the activity of NADH oxidase, oxidative stress SBP and aortic stiffness through inhibited NKA on endothelium membrane and induce depolarization. The weak link between MBG excretion, SBP and aortic pulsewave velocity indicated that these connections were associated with sodium intake. Although in the short term, the effect of MBG might balance the high salt load and slow the elevation of blood pressure (Mou et al., 2014), the vasoconstrictive effected by inhibiting NKA may be the long-term response of MBG. In addition, Dietary sodium restriction did not reduce level of plasma MBG (Jablonski et al., 2013).

Studies have found that MBG activated pre-fibrotic signal, which could activate various signaling pathways and EGFR signals by inhibiting NKA, leaded to degeneration of the left ventricular muscle fli-1 and inducing collagen -1 synthesis (Elkareh et al., 2009; Liu et al., 2012; Xie et al., 2013). Study found myocardial fibrosis and siginificant elevation of MBG level in rats with a minipump for infusing MBG and rats had uremia myocarditis (Elkareh et al., 2007). However, the anti-MBG antibody could reverse the myocardial fibrosis of the renal failure model and reduce the blood pressure of the pre-epileptic and salt-sensitive hypertension models (Fedorova et al.,

2008). Studies on normal rats suggested high-salt diet stimulated the production of MBG, which promoted tissue remodeling, especially the heart and kidneys, but not affected blood pressure. Giving hight-salt diet to rats with normal blood pressure induced vascular fibrosis through mechanisms of stress-dependence or MBG-dependence, and this damage could be relieved by immunonetralization of MBG antibody (Grigorova et al., 2016). The high salt diet not only increased the level of MBG, but also increased the collagen in aorta. Previous studies have proved that MBG started the myocardial pro-fibrosis signal in chronic renal failure model (Elkareh et al., 2007) and high-salt diet rat with normal blood pressure, plasma and urine MBG moderate elevated left ventricular muscle and kidney reconstruction, also moderated elevated plasma and urine MBG to induce left ventricular muscle and kidney reconstruction. Even if blood pressure did not changed in adult rats, in order to coped with a high-salt diet, MBG levels were still elevated and enhanced vascular fibrosis, which damaged vasodilation. Immunonetralization of MBG could reduce vascular fibrosis and restore vasodilation. Therefore, MBG plays an important role in inducing fibrosis and tissue reconstruction.

4 Conclusion

As people's attention to salt sensitive hypertension gradually increases, the understanding of the marinobufagenin becomes more and more thorough. Physiological and pathological role of marinobufagenin in the salt sensitive hypertension still needs to be confirmed further, which will help us learn more about this particular type of hypertension, meanwhile, provides more theoretical basis for its prevention.

Authors' contributions

Xiaoxiao Fang completed the writing of this thesis, and Xinghui Jing was responsible for the arrangement of literature. Junfeng Wang was responsible for the collection of the literature, and Yuan Gao was responsible for writing guidance.

Acknowledgments

This study was funded by the national natural science foundation (NSF) study on the activity and expression of Na^+/K^+-ATPase in kidney tubules regulated by lamina terminalis (31160214).

References

Anderson D.E., Fedorova O.V., Morrell C.H., Longo D.L., Kashkin V.A., Metzler J.D., Bagrov A.Y., and Lakatta E.G., 2008, Endogenous sodium pump inhibitors and age-associated increases in salt sensitivity of blood pressure in normotensives, Am J Physiol Regul Integr Comp Physiol, 294(4): 248-1254 https://doi.org/10.1152/ajpregu.00782.2007

Carey R.M., Schoeffel C.D., Gildea J.J., Jones J.E., McGrath H.E., Gordon L.N., Park M.J., Sobota R.S., Underwood P.C., Williams J., Sun B., Raby B., Lasky-Su J., Hopkins P.N., Adler G.K., Williams S.M., Jose P.A., Felder R.A., 2012, Salt sensitivity of blood pressure is associated with polymorphisms in the sodium-bicarbonate cotransporter. Hypertension, 60(5): 1359-1366 https://doi.org/10.1161/HYPERTENSIONAHA.112.196071

Elkareh J., Kennedy D.J., Yashaswi B., Vetteth S., Shidyak A., Kim E.G., Smaili S., Periyasamy S.M., Hariri I.M., Fedorova L., Liu J., Wu L., Kahaleh M.B., Xie Z., Malhotra D., Fedorova O.V., Kashkin V.A., Bagrov A.Y., and Shapiro J.I., 2007 ,Marinobufagenin stimulates fibroblast collagen production and causes fibrosis in experimental uremic cardiomyopathy, Hypertension,49(1): 215-224 https://doi.org/10.1161/01.HYP.0000252409.36927.05

Elkareh J., Periyasamy S.M., Shidyak A., Vetteth S., Schroeder J., Raju V., Hariri I.M., El-Okdi N., Gupta S., Fedorova L., Liu J., Fedorova O.V., Kahaleh M.B., Xie Z., Malhotra D., Watson D.K., Bagrov A.Y., and Shapiro J.I., 2009, Marinobufagenin induces increases in procollagen expression in a process involving protein kinase C and Fli-1: implications for uremic cardiomyopathy, Am J Physiol Renal Physiol, 296(5): 1219-1226 https://doi.org/10.1152/ajprenal.90710.2008

Fedorova O.V., Lakatta E.G., Bagrov A.Y., 2000, Endogenous Na,K pump ligands are differentially regulated during acute NaCl loading of Dahl rats, Circulation, 102(24): 3009-3014 https://doi.org/10.1161/01.CIR.102.24.3009

Fedorova O.V., Agalakova N.I., Talan M.I., Lakatta E.G., 2005, Brain ouabain stimulates peripheral marinobufagenin via angiotensin II signalling in NaCl-loaded Dahl-S rats, Hypertens, 23(8): 1515-1523 https://doi.org/10.1097/01.hjh.0000174969.79836.8b

Fedorova O.V., Zhuravin I.A., Agalakova N.I., Yamova L.A., Talan M.I., Lakatta E.G., Bagrov A.Y., 2007, Intrahippocampal microinjection of an exquisitely low dose of ouabain mimics NaCl loading and stimulates a bufadienolide Na/K-ATPase inhibitor, Hypertens, 25(9): 1834-1844 https://doi.org/10.1097/HJH.0b013e328200497a

Fedorova O.V., Zernetkina V.I., Shilova V.Y., Grigorova Y.N ., Bagrov A.Y., Lakatta E.G., 2015, Synthesis of an Endogenous Steroidal Na Pump Inhibitor Marinobufagenin, Implicated in Human Cardiovascular Diseases, Is Initiated by CYP27A1 via Bile Acid Pathway, Circ Cardiovasc Genet, 8 (5): 736-745

https://doi.org/10.1161/CIRCGENETICS.115.001217

Fedorova, O.V., Simbirtsev A.S., Kolodkin N.I., Kotov A.Y., Agalakova N.I., Kashkin V.A., Tapilskaya N.I., Reznik V.A., Frolova E.V., Nikitina E.R., Georgy V., Budny G.V., Dan L. Longo D.L., Lakatta E.G., Bagrov A.Y., 2008, Monoclonal antibody to an endogenous bufadienolide, marinobufagenin, reverses preeclampsia-induced Na/K-ATPase inhibition and lowers blood pressure in NaCl-sensitive hypertension, J Hypertens, 26 (12): 2414-25
https://doi.org/10.1097/HJH.0b013e328312c86a

Fedorova O.V., Lakatta E.G., Bagrov A.Y., Melander O., 2015, Plasma level of the endogenous sodium pump ligand marinobufagenin is related to the salt-sensitivity in men, J Hypertens, 33(3): 534-541
https://doi.org/10.1097/HJH.0000000000000437

Felder R.A., White M.J., Williams S.M., Jose P.A., 2013, Diagnostic tools for hypertension and salt sensitivity testing, Curr Opin Nephrol Hypertens, 22 (1): 65-76
https://doi.org/10.1097/MNH.0b013e32835b3693

Frame A.A., Wainford R.D., 2017, Renal sodium handling and sodium sensitivity, Kidney Res Clin Pract, 36 (2): 117-131
https://doi.org/10.23876/j.krcp.2017.36.2.117

Grigorova Y.N., Juhasz O., Zernetkina V., Fishbein K.W., Lakatta E.G., Fedorova O.V., Bagrov A.Y., 2016, Aortic Fibrosis, Induced by High Salt Intake in the Absence of Hypertensive Response, is Reduced by a Monoclonal Antibody to Marinobufagenin, Am J Hypertens, 29 (5): 641-646
https://doi.org/10.1093/ajh/hpv155

Jablonski K.L., Fedorova O.V., Racine M.L., Geolfos C.J., Gates P.E., Fleenor B.S., Lakatta E.G., Bagrov A.Y., Seals D.R., 2013, Dietary sodium restriction and association with urinary marinobufagenin, blood pressure, and aortic stiffness, Clin J Am Soc Nephrol, 8 (11): 1952-1959
https://doi.org/10.2215/CJN.00900113

Kotchen T.A., Cowley A.W., Jr, Frohlich E.D., Salt in health and disease--a delicate balance, N Engl J Med, 27;368 (26): 2531-2532

Liang M., Tian J., Liu L.J., Pierre S., Liu J., Shapiro J., Xie Z.J., 2007, Identification of a pool of non-pumping Na/K-ATPase, J Biol Chem, 282 (14): 10585-10593
https://doi.org/10.1074/jbc.M609181200

Liu C., Bai Y., Chen Y., Wang Y., Sottejeau Y., Liu L., Li X., Lingrel J.B., Malhotra D., Cooper C.J., Shapiro J.I., Xie Z.J., Tian J., 2012, Reduction of Na/K-ATPase potentiates marinobufagenin-induced cardiac dysfunction and myocyte apoptosis, J Biol Chem, 287 (20): 16390-16398
https://doi.org/10.1074/jbc.M111.304451

Morrill G.A., Kostellow A.B., Askari A., 2008, Progesterone binding to the alpha1-subunit of the Na/K-ATPase on the cell surface: insights from computational modeling, Steroids, 73 (1): 27-40
https://doi.org/10.1016/j.steroids.2007.08.012

Mou J.J., Ren K.Y., 2012, Salt sensitivity diagnosis and mechanism of high blood pressure Theory and practice of diagnostics, 11 (06): 543-546

Mou J.J., Pei Z.R., Liu F.Q., Zhu C.,Wang L., 2014, Salt sensitivity of patients with high blood pressure circadian rhythm of blood pressure variability and urinary sodium excretion, Chinese Journal of Cardiovascular Medicine, 19 (1): 28-31

Schoner W., Scheiner-Bobis G.., 2007, Endogenous and exogenous cardiac glycosides: their roles in hypertension, salt metabolism, and cell growth, Am J Physiol Cell Physiol, 293 (2): 509-536
https://doi.org/10.1152/ajpcell.00098.2007

Wang Y., Suo L.Y., Li X.M., 2011, Endogenous digitalis relationship with cardiovascular disease research status, Chinese journal of cardiovascular, 16(4): 322-324

Xie, J.X., Li X, Xie Z., 2013, Regulation of renal function and structure by the signaling Na/K-ATPase. IUBMB Life, 65 (12): 991-998
https://doi.org/10.1002/iub.1229

Xu Z.S., 2015, Salt sensitivity of blood pressure fluctuations in patients with high blood pressure and clinical observation and urinary sodium excretion, Cardio-cerebrovascular disease prevention and control, 15 (4): 281-283,295

Yoshinaga M., Toda N., Tamura Y., Terakado S., Ueno M., Otsuka K., Numabe A., Kawabata Y., Uehara Y., 2012, Japanese traditional miso soup attenuates salt-induced hypertension and its organ damage in Dahl salt-sensitive rats, Nutrition, 28 (9): 924-931
https://doi.org/10.1016/j.nut.2011.09.010