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The role of Akt and sigma-1 receptor signalingin the progression of cardiac hypertrophy and cardiomyopathy

著者	BHUIYAN MD. SHENUARIN
学位授与機関	Tohoku University
学位授与番号	薬博第437号
URL	http://hdl.handle.net/10097/51095

氏　名（国籍）	ブイヤン　エムディ　シェニュアリン BHUIYAN MD. SHENUARIN
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学位論文題目

The role of Akt and sigma−1 receptor signaling in the progression of cardiac hypertrophy and cardiomyopathy
（心筋肥大と心筋障害の進展における Akt 及び Sigma−1 受容体シグナルの役割）

論文審査委員	（主　査）教　授	福永浩司
	教　授	今井　潤
	教　授	青木淳賢

論 文 内 容 要 旨

Cardiovascular disease (CVD) is one of the leading causes of death worldwide, accounting for 16.7 million deaths per annum according to the World Health Organization. CVD encompasses a wide spectrum of cardiac pathologies including 5.3 million people living with heart failure in the USA alone and this value is expected to double by the year 2030 as the "baby boomer" generation ages. Heart failure develops as a result of prolonged stress which can be caused by numerous conditions including myocardial infarction, valve defects and hypertension. These conditions initially place the heart under stress which induces adaptive cardiac hypertrophy. However, over time the stress leads to maladaptive hypertrophy, ventricular dilation and contractile impairments such as systolic dysfunction. Although much effort has been directed toward understanding the mechanism underlying heart failure progression and developing therapeutic approaches to treat and/or prevent heart failure, there still is no cure available. Because of limitation of current therapies for heart failure, the mortality for heart failure patients is extremely high with patients only having a 50% chance of surviving 3 to 5 years after diagnosis. Therefore, additional studies are required to increase understanding of the therapeutic targets and the signals involved in loss of cardiac function during progression of heart failure. The main achievements of my research are summarized below.

1. Targeting Akt for cardioprotection by vanadium compounds on myocardial ischemia/reperfusion-induced injury. In the cardiovascular system, Akt, also named protein kinase B plays critical roles in the regulation of cardiac hypertrophy, angiogenesis, and apoptosis. Firstly, I found that Akt signaling is significantly impaired in rat heart following myocardial ischemia-reperfusion (MIR) injury with concomitant deregulation of the downstream Akt pathways. To rescue heart from MIR-induced injury and contractile dysfunction, I introduced a novel Akt activator, bis(1-oxy-2-pyridinethiolato)oxovanadium (IV) [VO(OPT)]. The VO(OPT) administration in MIR model rats upregulated Akt signaling in the cardiomyocytes and significantly reduced the ischemia-induced infarction (Fig. 1). Akt activation induced phosphorylation of proapoptotic protein Bad, thereby reducing mitochondria-dependent apoptosis. Moreover, VO(OPT) treatment abolished dephosphorylation of forkhead transcription factors after

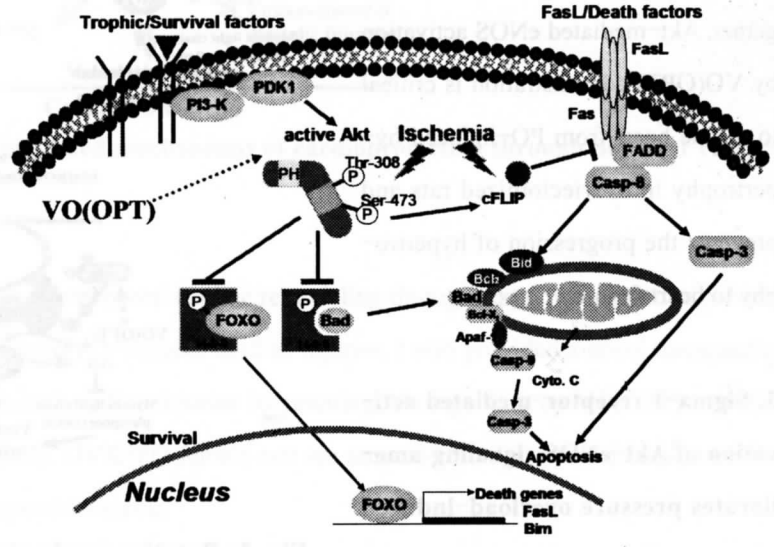

Fig. 1: Putative mechanism of myocardial protection by VO(OPT).

ischemia/reperfusion injury, thereby inhibiting expression of Fas ligand and Bim. Furthermore, VO(OPT) treatment after ischemia/reperfusion promoted expression of FLIP through Akt activation, thereby further inhibiting activation of Fas/Fas-ligand intracellular signal (Fig. 1). Taken together, VO(OPT) treatment during ischemia/reperfusion is likely beneficial as a cardioprotective drug in subjects undergoing reperfusion therapy following a myocardial infarction.

2. A novel rat model of postmenopausal myocardial hypertrophy with impaired Akt-mediated eNOS signaling. Secondly, I documented that the pathological hypertrophy induced by pressure overload causes an inactivation of Akt signaling in the heart. I introduced a novel heart injury model using ovariectomized (OVX) and pressure overloaded (PO) female rats, which is attractive model for testing cardioprotective drugs in hypertension-induced cardiac injury in postmenopausal women. Using this model, I confirmed that ovariectomy aggravates pressure overload-induced hypertrophy. The cardiac injuries in OVX-PO rats were associated with impairments of both Akt and Akt-mediated eNOS signaling pathways (Fig. 2). Interestingly, rats subjected to OVX-PO were unable to compensate cardiac dysfunction following hypertrophy, thereby increasing mortality following repeated injection of isoproterenol. To confirm the causative role of impaired Akt-mediated eNOS signaling in OVX-PO-induced cardiomyopathy, the OVX-PO rats were administered with VO(OPT) for two weeks after OVX-PO surgery. The VO(OPT) administration significantly restored the reduced Akt activity and increased Akt-mediated eNOS activation (Fig. 2). The VO(OPT)-induced eNOS activation also ameliorated left ventricular (LV) contractile dysfunction, thereby reducing mortality following repeated injection of isoproterenol. Taken together, Akt-mediated eNOS activation by VO(OPT) administration is critical to rescue heart from PO-induced hypertrophy in ovariectomized rats and prevents the progression of hypertrophy to heart failure.

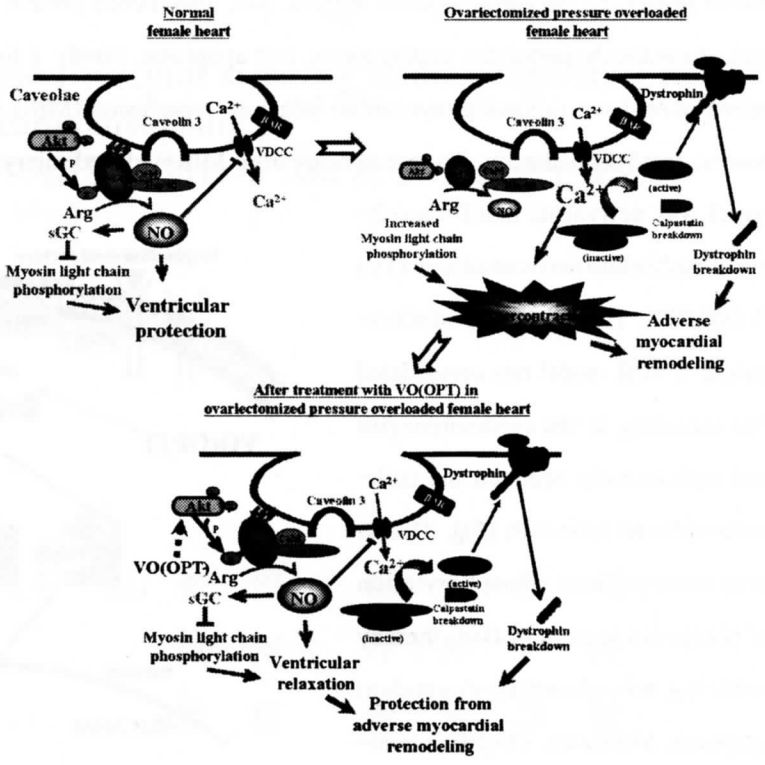

Fig. 2: Putative mechanism of postmenopausal hypertrophy and cardioprotective action of VO(OPT)

3. Sigma-1 receptor-mediated activation of Akt-eNOS signaling ameliorates pressure overload-induced hypertrophy and dysfunction. Sigma-1 receptor (Sig-1R) is widely

expressed as integral membrane protein with two transmembrane domains. The physiological relevance of the enigmatic Sig-1R in heart remains unclear. To clarify the physiological and pathological role of Sig-1R on the heart function, I first observed the expression of Sig-1R in normal rat heart and also in pathological condition, mainly PO-induced hypertrophy in OVX rats. I demonstrated, for the first time, the potential role of Sig-1R expression in the heart to attenuate PO-induced hypertrophy in OVX rats. Sig-1R expression decreased time dependently along with progression of cardiac hypertrophy with significant decreased expression observed 4 weeks after OVX-PO. To confirm the cardioprotective role of Sig-1R on the heart against PO-induced hypertrophy, I treated the rats with the endogenous ligands for Sig-1R. Neurosteroid dehydroepiandrosterone (DHEA), also known as Sig-1R agonist, elicited Sig-1R upregulation and stimulated Sig-1R-mediated activation of the Akt-eNOS signaling in hypertrophied cardiomyocytes in OVX-PO rats (Fig. 3). Moreover, DHEA could protect the kidney and aortic endothelial cells via stimulation of the Akt signaling pathway. Thus, as Akt signaling is downstream of Sig-1R, Sig-1R-mediated eNOS activation is essential to attenuate PO-induced cardiac hypertrophy and injury (Fig. 3).

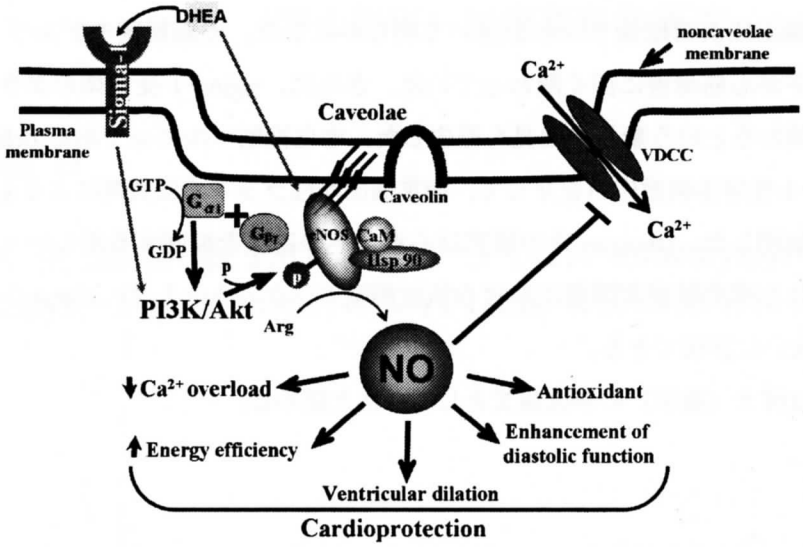

Fig. 3: Schematic presentation of DHEA-mediated mechanisms of cardioprotection through Sigma-1 receptor

In summary, I proposed novel mechanisms of detrimental cardiac remodeling through Akt downregulation, which accounts for cardiac decompensation in MIR- and PO-induced cardiac injuries. I also provided a novel therapeutic strategy for ischemia- and hypertension-induced cardiac injuries by rescuing Akt signaling by VO(OPT) and elevating Sig-1R/Akt signaling by DHEA. Finally, OVX-PO female rats are attractive model to test therapeutics for cardiovascular events especially in postmenopausal women.

審 査 結 果 の 要 旨

循環器障害である高血圧，狭心症，不整脈などに対する有効な治療薬が開発されているにも拘らず，心臓疾患は全世界において死亡原因のトップである。特に，心臓肥大から心不全に進展するメカニズムの解明と致死的な心不全の治療法は未だ確立されていない。従って，心不全進展のメカニズムと治療薬の開発が重篤な心臓疾患を持つ患者の治療と QOL を高めるために必要である。本研究では 1) 冠状動脈の虚血再灌流ラットを用いて新規心臓保護薬バナジウム有機錯体の心筋保護作用とそのメカニズムを明らかにした。2) 卵巣摘出雌性ラットを用いて，圧負荷による心筋障害に protein kinase B (Akt) と内皮型一酸化窒素合成酵素 (eNOS) の機能低下が関わることを明らかにした。3) 卵巣摘出圧負荷雌性ラットにおける心筋障害に対して sigma-1 受容体のアゴニストが有効な治療薬となることを明らかにした。

Akt は種々細胞の生存に必須の働きをしている。Bhuiyan 氏は心筋梗塞ラットの心臓で Akt 活性が顕著に減少すること，その結果 Akt により活性化される eNOS の障害が起こることを明らかにした。本研究はバナジウム有機錯体が心臓において Akt を活性化して eNOS 障害を抑制すること，同時に，心筋の梗塞サイズも有意に縮小することを証明した。次に，閉経後の女性での高血圧による循環器障害のメカニズムについて卵巣摘出圧負荷雌性ラットを用いて明らかにした。心筋梗塞モデルラットと同様に，Akt と eNOS の機能低下が心筋障害に深く関わっていた。さらに，sigma-1 受容体のダウンレギュレーションも心機能障害に関わるという新しい知見も報告した。老化抑制ホルモンである dehydroepiandrosterone (DHEA) が sigma-1 受容体刺激作用を介して，卵巣摘出雌性ラットの圧負荷による心機能障害を完全に回復させることを証明した。Bhuiyan 氏の研究は心不全への進展を抑制する新しいリード化合物を創出したことに加えて，心疾患治療薬開発における新規創薬ターゲットとして，sigma-1 受容体を世界で初めて見出した点で大いに評価できる。

よって，本論文は博士 (薬学) の学位論文として合格と認める。