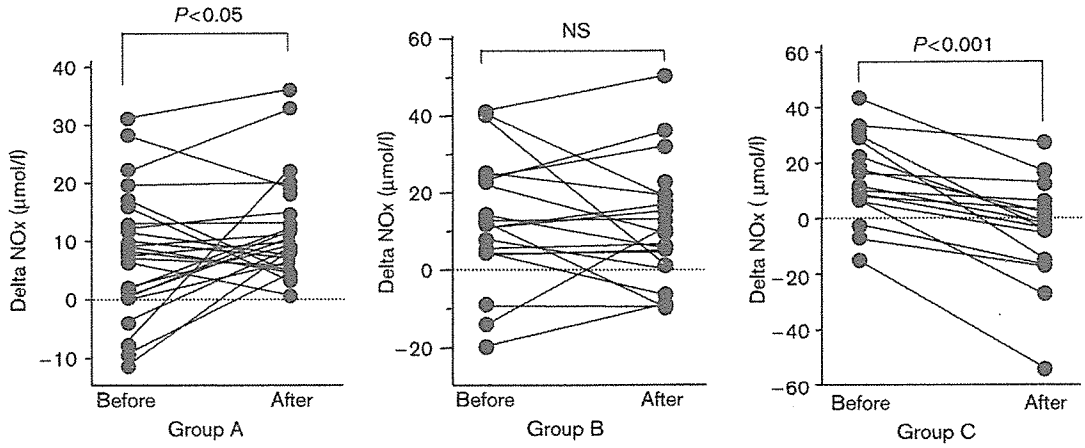
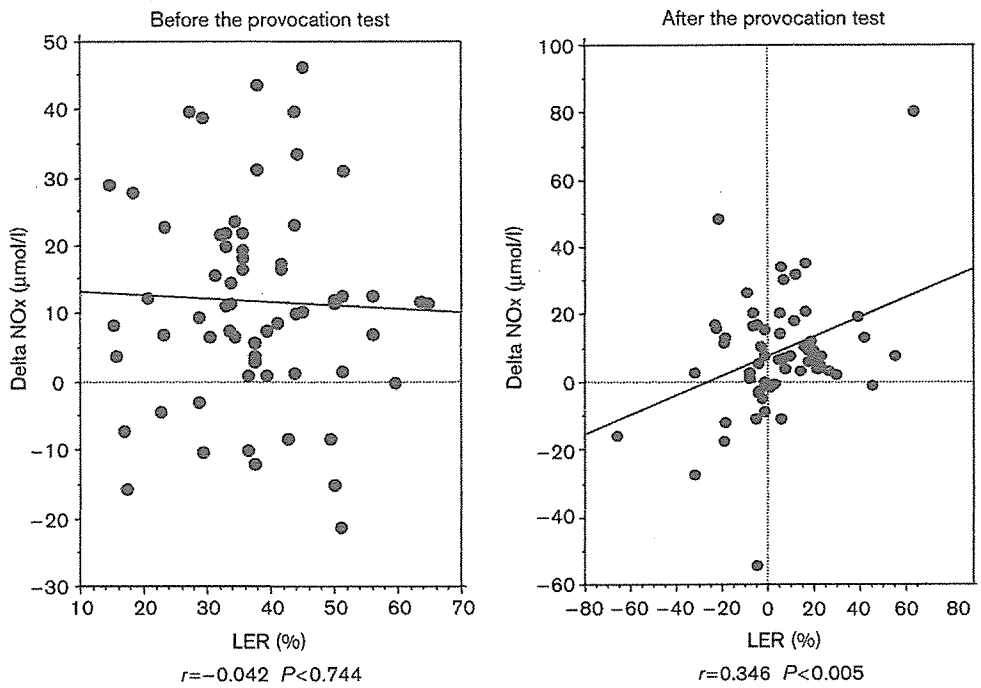
Fig. 2



Delta nitrite/nitrate (NOx) levels before and after an intracoronary injection of acetylcholine in groups A, B and C. The delta NOx indicates the difference in serum NOx level between the coronary sinus (CS) and the aorta (Ao) [delta NOx (CS–Ao)].

Fig. 3



Correlation between delta nitrite/nitrate (NOx) levels [coronary sinus (CS)–aorta (Ao)] and lactate extraction ratio (LER) before (left) and after (right) an intracoronary injection of acetylcholine.

We have reported that the −786T > C polymorphism enhanced the vasoconstriction response due to an intracoronary injection of ACh [9,16]. We suggested that reducing the ACh-induced NO production from the coronary endothelial cells in the patients with the −786T > C polymorphism causes significant

vasoconstriction. Although the ACh-induced NO is mainly generated by the endothelial cells, both endothelial cells and cardiomyocytes are thought to be potential sources of NO generation when a state of hypoxia exists in the heart. Node *et al.* [17] reported that NO production from the heart is increased in ischemic hearts, and after exertion, in patients with effort angina. These results suggest that hypoxia possibly accounts for an increase in NO production from the heart, including from coronary arterial endothelial cells and/or from cardiomyocytes. Han *et al.* [18] reported that hypoxic red blood cells (RBCs) generate HbFe(II)NO, and that the NO consumption rate therefore increases. The NO level is possibly reduced under the hypoxic condition because of an increase in the NO consumption rate of RBCs. In the present study, for non-coronary spasm patients with the –786T/T genotype (group A), NO was possibly generated from endothelial cells due to the intracoronary injection of ACh; furthermore, their coronary arteries did not produce coronary spasm. In coronary spasm patients with the –786T/T genotype (group B), an intracoronary injection of ACh caused coronary spasm. Although the NO consumption rate possibly increases in hypoxic RBCs, the total NO level in the serum was maintained at an overall high level in group B. The increase in NO production from the heart, including from the endothelial cells and/or from the cardiomyocytes, under an ischemic condition, immediately relaxed the coronary arteries. After an intracoronary injection of ACh, there was no significant difference in the delta NOx levels between groups A and B. Although the coronary spasm patients with the –786T/T genotype have high delta NOx levels before and after the provocation test, some of them possibly have coronary spasm for reasons other than the reduced NO production from the heart. In coronary spasm patients with the –786C allele (group C), reduced NO production from the endothelial cells due to the intracoronary injection of ACh caused coronary spasm, and an insufficient supply of NO production from the heart under this ischemic condition prolonged coronary spasm. An increase in the NO consumption rate in hypoxic RBCs possibly leads to a still more critical spasm state. Previously, we reported that the –786T > C polymorphism is strongly associated with coronary spasm and also with myocardial infarction without organic stenosis [19]; furthermore, we suggested that this polymorphism is possibly associated with the severity of coronary spasm. The –786T > C polymorphism reduced NO production from the heart, even in an ischemic condition, and predisposed the patients to a prolonged coronary spasm, leading to myocardial infarction without organic stenosis. Also, endothelial dysfunction and oxidative stress are known to be crucially involved in the pathogenesis of coronary spasm [20–24]. A decrease in NO production possibly increases oxidative stress and predisposes the patients with the –786C allele to coronary spasm.

There are some reports regarding systemic circulating NOx levels and the –786T > C polymorphism [10,25,26]. Although there is a low tendency for the systemic circulating NOx level in subjects with the –786C allele, there are few reports stating that it is clearly low. It is possible that there is not enough of a significant difference in the systemic circulating NOx level to classify this as being due to the genotype of the –786T > C polymorphism because of the influences of either meal and/or individual levels of oxidative stress. In the present study, an intracoronary injection of ACh significantly increased delta NOx levels in subjects without coronary spasm without the –786C allele, although it did not significantly change the delta NOx levels in subjects with coronary spasm without the –786C allele, and it significantly decreased the delta NOx level in subjects with coronary spasm with the –786C allele. There was a difference of sufficient magnitude in delta NOx levels before and after the provocation test to classify the genotype of the –786T > C polymorphism, even in coronary spasm patients. It is well known that NO plays a key role in the regulation of vascular tone [4,5,27,28] and has vasoprotective effects by scavenging superoxide radicals and suppressing platelet aggregation, leukocyte adhesion and smooth muscle cell proliferation [29–31]. A decrease in the delta NOx level possibly affects the cardiovascular system and leads to severe vasoconstriction. Furthermore, Tanus-Santos *et al.* [32] reported that the –786C allele decreases platelet-derived NO. The –786C allele may accelerate platelet aggregation and serve as a risk factor for cardiovascular disease. Indeed, it was reported that the –786C allele is associated with coronary spasm [8], myocardial infarction [19] and coronary organic stenosis [33].

In conclusion, the –786T > C polymorphism reduces NO production from the heart due to an intracoronary injection of ACh, and thus predisposes patients to a prolonged and more severe coronary spasm.

Study limitation

In the present study population, there were two non-coronary spasm patients with the –786C/T genotype and there were no patients with the –786C/C genotype, this is possibly because the study population was relatively small in size. However, we have previously reported that the frequencies of these patients are relatively low in the Japanese population [8,9,19]. In both patients with the –786C/T genotype without coronary spasm, delta NOx levels basically decreased after the provocation test. Even in the case of non-coronary spasm patients, the –786C allele possibly suppresses NO production from the heart, which is due to an intracoronary injection of ACh. Further studies in a larger population group, including many non-coronary spasm patients with the –786C allele and many patients with the –786C/C genotype, will be beneficial to further elucidate this topic.

NO is generated by NO synthase (NOS), which exists as a family of related but distinct isoforms, including neuronal (nNOS) [34,35], inducible (iNOS) [36,37], and endothelial (eNOS) [4] isoforms. It has been reported that eNOS is detected in the endothelial cells overlying normal human aortas, fatty streaks and advanced atherosclerotic lesions, whereas iNOS and nNOS are not detectable in normal vessels, although widespread production of these two isoforms has been found in early and advanced lesions associated with macrophages, endothelial cells and mesenchymal-appearing intimal cells [38]. In the present study, we did not distinguish which isoform of NOS produces NO from the heart before or after the provocation test.

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III. 発症機序

メタボリックシンドローム発症にかかわる遺伝子異常

メタボリックシンドロームと11β-HSD1遺伝子多型

Metabolic syndrome and 11β-hydroxysteroid dehydrogenase type 1 gene polymorphisms

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Key words：メタボリックシンドローム，11β-HSD1，遺伝子多型，内臓脂肪

はじめに

11β-hydroxysteroid dehydrogenase type 1（11β-HSD1）は不活性化コルチゾンを活性化コルチゾールに変換する酵素である．11β-HSD1は肝臓や脂肪組織，筋肉，膵臓，生殖腺，脳など多くの組織に存在している[1]．11β-HSD1が末梢組織でのグルココルチコイド濃度を変えることで，肥満やインスリン抵抗性，2型糖尿病の病態にも関与していると考えられる．

本稿では，11β-HSD1の遺伝子多型についてのこれまでの知見と著者らの検討した成果を概説する．

1. メタボリックシンドロームと11β-HSD1

メタボリックシンドロームは肥満を中心とし，高血圧，脂質代謝障害，耐糖能異常を呈する症候群である．一方，グルココルチコイド過剰（いわゆるCushing症候群）は肥満，高血圧，耐糖能異常を来すことから，グルココルチコイド過剰とメタボリックシンドロームとの類似性が考えられる．しかし，肥満やメタボリックシンドロームの患者では血中コルチゾール濃度が決して高くはなく，これまで直接の関係はないと考えられていた．また，コルチゾールがグルココルチコイド受容体やミネラルコルチコイド受容体に結合する末梢組織においては11β-HSD1がコルチゾール活性を調整していることが知られている（**図1**）[2]．特に，脂肪組織の11β-HSD1は肥満に伴うインスリン抵抗性の病態に重要な役割を有している．耐糖能障害のない単純性肥満の場合には内臓脂肪蓄積に伴い代償的に11β-HSD1活性が低下し，そのことが肝臓における糖新生を抑え脂肪細胞の分化を抑制しているが，肥満を伴う2型糖尿病などではその代償が起こらず，内臓脂肪蓄積によりインスリン抵抗性の亢進や肝臓の糖新生亢進，脂肪細胞の分化促進を来す（**図2**）[3]．更に，ピマインディアンおよび白人における検討で，脂肪細胞の11β-HSD1の遺伝子発現と蛋白活性が肥満と関連しているという報告がある（**表1**）[4]．モデル動物を用いた検討でも脂肪組織に11β-HSD1を過剰発現させたマウスにおいては過食，内臓脂肪肥満，高血糖，高インスリン血症，耐糖能異常，インスリン抵抗性，高脂血症がみら

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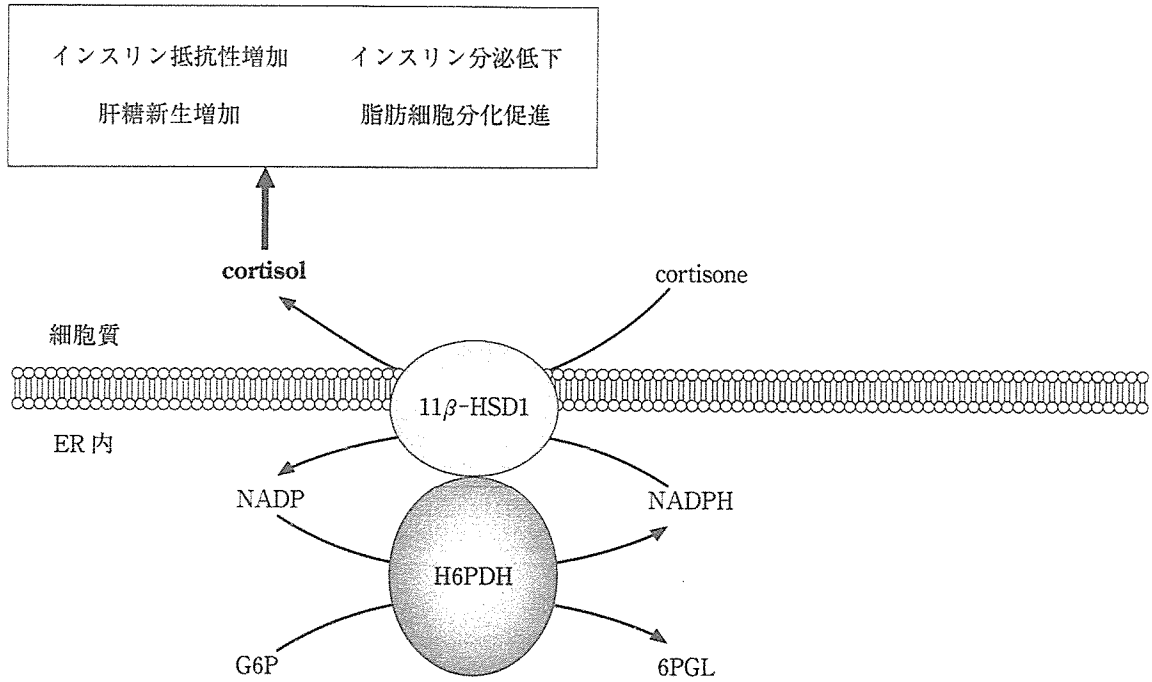

図1 11β-HSD1は細胞内でコルチゾンをコルチゾールに変換し，糖代謝やインスリン抵抗性に関与する(Tomlinson JW: Nat Clin Pract Endocrinol Metab 1: 92-99, 2005より改変)

6PGL: 6-phosphogluconolactonate, 11β-HSD1: 11β-hydroxysteroid dehydrogenase type 1, ER: endoplasmic reticulum, G6P: glucose-6-phosphate, H6PDH: hexose-6-phosphate dehydrogenase, NADP: nicotinamide adenine dinucleotide phosphate, NADPH: nicotinamide adenine dinucleotide phosphate, reduced form.

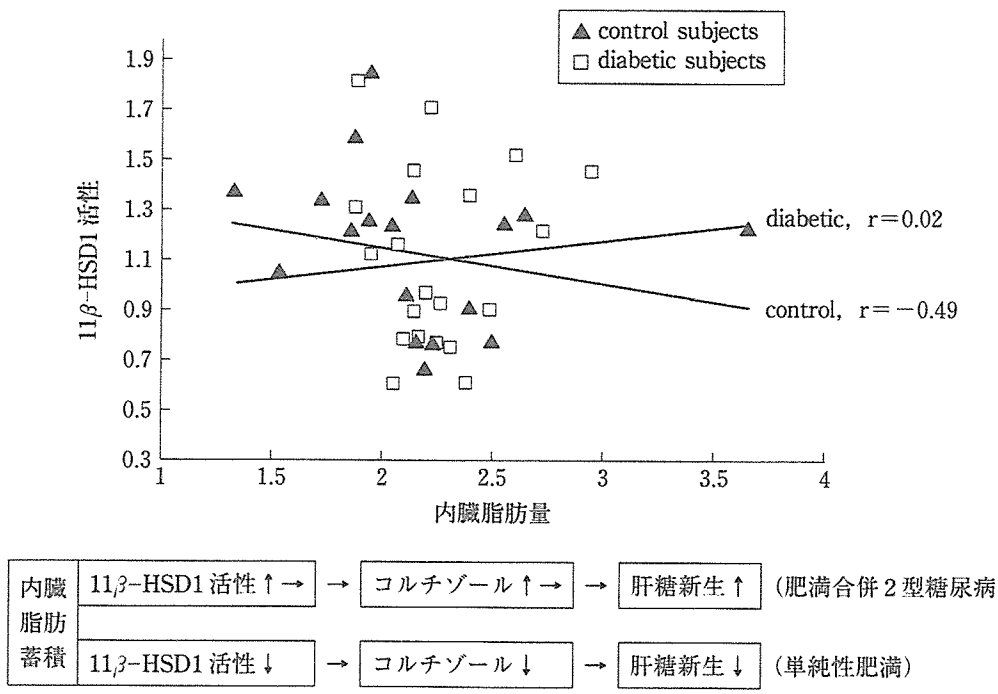

図2 内臓脂肪量と11β-HSD1活性の関連(文献[3]より改変)

表1 脂肪組織の11β-HSD1活性，遺伝子発現量，コルチゾール値と各代謝指標との相関
（文献[4]より改変）

	11β-HSD1活性	11β-HSD1 mRNA	脂肪組織コルチゾール
体格指数BMI	0.68*	0.34*	0.29
体脂肪率%fat	0.48*	0.15	0.22
waist(n=27)	0.52*	0.26	0.21
空腹時血糖	0.43*	0.19	−0.28
2時間血糖	0.08	0.09	−0.19
空腹時インスリン	0.60	0.42	0.37
HOMA-IR	0.70*	0.46*	0.30

各数字は相関係数(r)，*$p<0.05$.

表2 11β-HSD1遺伝子多型と疾患との関連が検討されたもの

疾患	11β-HSD1遺伝子多型	関連性	文献
Alzheimer病	5′領域ハプロタイプ	あり	a)
認知障害	rs846911，rs12086634	なし	b)
多嚢胞性卵巣症	83557insA	なし	c)
多嚢胞性卵巣症	rs12086634	あり	d)
2型糖尿病	rs846910，rs12086634	あり	e)
メタボリックシンドローム	4478T>G，4437-4438insA，10733G>C	なし	f)

a) de Quervain DJF, et al: Hum Mol Genet **13**: 47-52, 2004.
b) Deary IJ, et al: Neurosci Lett **393**: 74-77, 2006.
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れた[5]．また，11β-HSD1遺伝子欠損マウスにおいては，肝臓の糖新生関連酵素の減少があり，肝臓のインスリン感受性が増し，食後高血糖になりにくいことが報告されている[6]．ヒトにおいても肥満がない耐糖能障害の患者においては脂肪組織の11β-HSD1活性は増加しておらず肝臓の11β-HSD1活性も正常と変わらないが，肥満者においては肝臓の11β-HSD1活性が低下していることが報告されている[7]．このように，脂肪組織以外の11β-HSD1活性も肥満におけるインスリン抵抗性に寄与している．更に，興味深いことに膵臓の11β-HSD1活性が低下すると，膵β細胞からのインスリン分泌が増加することが報告されている[8]．このように病態において11β-HSD1の発現や活性が異なる調整を受けていることが示唆され，11β-HSD1が2型糖尿病やメタボリックシンドロームの発症・進展に重要であると考えられる．

2. 11β-HSD1の遺伝子多型

11β-HSD1遺伝子は1q32-q41染色体に存在し，そのアイソフォームであり機能が異なる11β-HSD2遺伝子は16q22染色体に存在する．11β-HSD1遺伝子は6個のエクソンからなり，9kb以上の大きさがある．これまでに幾つかの11β-HSD1遺伝子多型と疾患との関連が報告されている(表2)．Alzheimer病と11β-HSD1遺伝子の転写調節領域の遺伝子多型のハプロタイプが関連するという報告があり，そのハプロタイプでは転写活性が低下しているとの報告がある[9]．

3. メタボリックシンドロームと 11β-HSD1 遺伝子多型

11β-HSD1 遺伝子の変異が原因となりコルチゾンからコルチゾールへの活性化不全が副腎皮質刺激ホルモンの増加を来し，そのためにアンドロゲン過剰症を来し，多嚢胞性卵巣症のような病態を呈することが報告されている[10]．多嚢胞性卵巣症の患者はインスリン抵抗性があり，2型糖尿病になりやすく，肥満者に多いことなどが知られており，11β-HSD1 遺伝子と2型糖尿病や肥満との関連が示唆された．肥満と11β-HSD1 遺伝子の多型についての検討では，11β-HSD1 遺伝子の5′隣接領域およびイントロンの遺伝子多型と肥満との関連はなく(ピマインディアン)[11]，マイクロサテライトやSNPを用いた他の検討でも同様の結果であった[12,13]．

これまで日本人において11β-HSD1 遺伝子について大規模症例を用いた検討はなかった．著者らは吹田市住民コホートを用いた研究で，女性のメタボリックシンドロームと11β-HSD1 遺伝子+27447G>C 多型が有意な関連を示すことを見いだした．特に女性の空腹時血糖は+27447C アリルを有する場合に高かった(図3)．これらの有意な関連は男性では認められず，性差が存在したがその理由については不明である．ただし，11β-HSD1 遺伝子多型と多嚢胞性卵巣症の関連が当然であるが女性においてみられていることはその点で興味深い．また，著者らの検討でも高血圧との関連はみられなかった．これは11β-HSD1 の活性化が細胞内のコルチゾールを増やし，血清コルチゾール値とは関係しないことがその理由であるかもしれない．

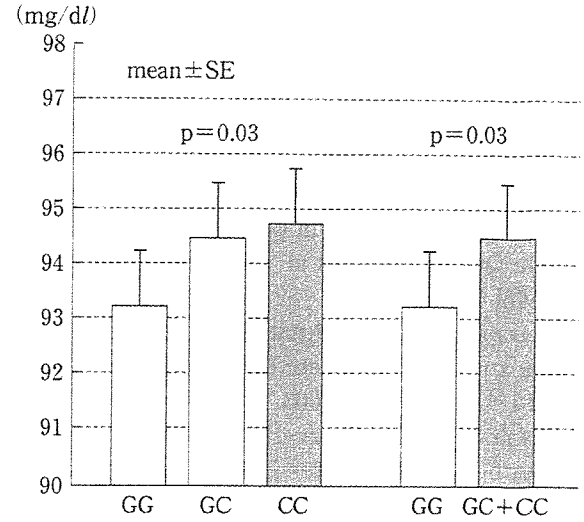

図3 11β-HSD1 遺伝子の+27447G>C SNP と空腹時血糖との関連(女性)

対象：糖尿病の既往がなく，糖尿病の内服治療を受けていないもの．

統計：共分散分析，調整変数として年齢，喫煙，飲酒，既往歴(高血圧，高脂血症)．

おわりに

メタボリックシンドロームは現代社会の生活習慣を反映し，心筋梗塞や脳卒中などの動脈硬化性疾患の原因となっている．しかし，生活習慣に対する身体の適応力や病気の易発症性は個人により異なる．11β-HSD1 遺伝子の多型がその個人差と関連している可能性が示唆されており，今後とも更に詳細な検討が必要と考えられる．

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