様式Ｃ－１９

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研究課題名（和文）　腎臓膜輸送体を制御する新規細胞内刺激伝達系の解明

研究課題名（英文）　A novel WNK signal cascade regulating renal transporters

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研究成果の概要（和文）：我々は、遺伝性高血圧症である偽性低アルドステロン症 II（PHAII）の原因遺伝子である WNK キナーゼのシグナル伝達系を、Wnk4$^{D561A/+}$PHAII 病態モデルを用いて明らかにした(Cell Metab 2007)。本研究は、PHAII 以外にこの新規 WNK キナーゼシグナルカスケードが生体内でもつ病態生理学的意義を明らかにすることを目的として行われた。その結果、WNK キナーゼを制御する液性因子や下流で制御される新たな輸送体を同定し、生体内における WNK キナーゼの血圧調整における重要な役割とその制御機構を明らかにした。

研究成果の概要（英文）：In 2007, we discovered a novel signal cascade of WNK kinases, and clarified that its constitutive activation causes human hypertension in pseudohypoaldosteronism type II (PHAII). This study was conducted to further clarify the roles of WNK signal cascade in vivo other than PHAII by using the genetically engineered mice. As a result, we were able to identify several hormonal factors that regulate WNK kinases and new downstream targets, and could provide a whole picture of WNK kinase signaling in the body, especially in kidney.

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１．研究開始当初の背景

腎臓は生体内での水・電解質環境維持にとって最も重要な臓器である。腎臓の中でその機能を最終的に担うのは、腎臓の尿細管各部位における水・電解質輸送体蛋白である。我々は 1990 年代のはじめに腎臓に存在する膜輸送体の分子同定を開始し、AQP 水チャネル（*Nature 1993* など）、CLC クロライドチャネル（*JBC 1993, Neuron 1994* など）などを数多くのチャネル分子をクローニングし、その生理的役割を明らかにすべく腎臓内での発現部位の同定や機能解析、またヒトでのこれら輸送体病の発見(*Am J Hum Genet, 2001*)やノックアウトマウス作成(*Nature Genet. 1999* など)を行ってきた。このような研究を通して腎臓膜輸送体自体に関する情報は飛

躍的に増加してきた。しかしながら、腎臓本来の持つ生体恒常性維持機構が達成されるためには、生体の置かれた環境が変化した時、例えば摂取塩分量や水分量が変化したとき、いかにしてそのシグナルがこれら膜輸送体に伝わり、その機能を調節しているかを明らかにしなくてはならない。

最近我々は偽性低アルドステロン症 II 型（以下 PHAII）のモデルマウスを作成し解析を行った。なぜ PHAII に注目したかという理由は、①PHAII の病態として我々が今まで研究してきた遠位尿細管に存在する膜輸送体分子の異常、特にクロライド輸送の異常が想定されていたこと（クロライドシャント説）。②PHAII は高血圧を呈する遺伝病であり、この疾患の病態生理の解明はより一般的な本態性高血圧症の病態解明に役立つと考えられること。③ポジショナルクローニングにより同定された PHAII の原因遺伝子は膜輸送体自体ではなく機能未知のリン酸化酵素 WNK キナーゼであった。この事実は、今までほとんどその実体が不明であった膜輸送体分子の新たな制御因子が genetic なエビデンスをもって同定さえたことを意味し、上記の研究目的の標的分子として最適であると考えられた。このように WNK キナーゼの生理的役割、PHAII における病態を明らかにすることで、腎臓における新たな輸送体制御のシグナル伝達系が明らかになると考えられた。

２．研究の目的

PHAII モデルマウスの解析で明らかになった WNK-OSR1/SPAK-NaCl 共輸送体シグナル伝達系の生体内での役割を確定し、PHAII 以外の病態への関与を探る。

３．研究の方法

WNK-OSR1/SPAK-NCC シグナル伝達系の各分子のノックアウトマウスを作成し、生体内で実際にシグナル伝達を行っているか解明する。さらに、WNK キナーゼの上流の制御因子の同定による PHAII 以外の病態への関与を探る。さらに腎臓の NaCl 出納調節以外の役割を探索するため、NCC 以外で WNK-OSR1/SPAK 系により制御される分子を KO マウスの phenotype を手がかりに同定する。

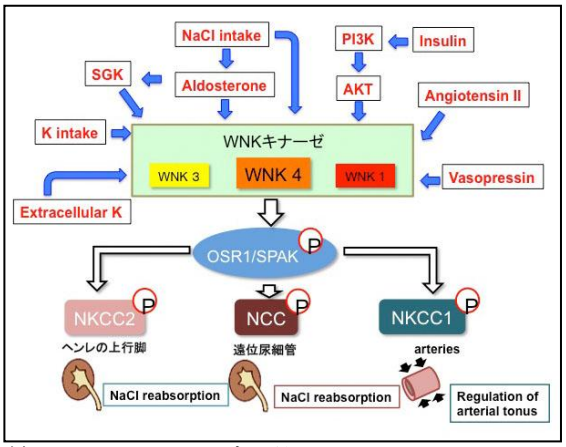
４．研究成果

１）WNK シグナル系の全貌の解明。

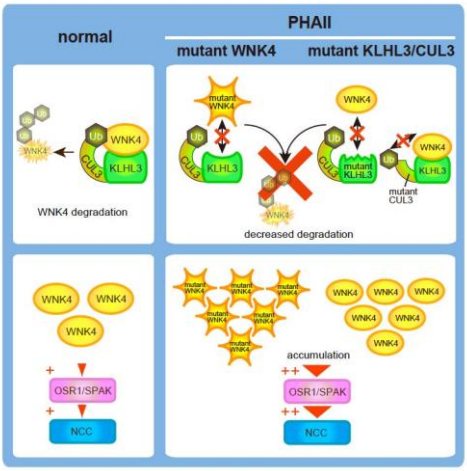
WNK-OSR1/SPAK シグナル系が実際に生体内でも機能していることを、WNK4 の低形成マウスの作成と解析 [28]、WNK キナーゼからのリン酸を受けないようにした SPAK および OSR1 のノックインマウスの解析 [11] を通じて証明した。その他、上流の各種制御因子の同定、下流では NCC 以外に NKCC1, NKCC2 がやはり OSR1/SPAK キナーゼにより制御を受けていること、特に NKCC1 は血管平滑筋のトーヌス調節に関わっている事を明らかにし、このシグナル系が血圧制御にかぎっても、単に腎臓での NaCl 出納調節だけにかかわっているのではなく、血管にも働くことで血圧制御に関わっている事が明らかとなった。

以下に、現時点で明らかとなった WNK キナーゼの制御因子や WNK-OSR1/SPAK シグナルが制御する分子をまとめた。

２）WNK の分解を司る新たな制御系の発見。



最近、WNK キナーゼ以外に KLHL3 と Cullin3 の遺伝子異常が同じ PHAII を引き起こす事が明らかとなった。PHAII を引き起こす WNK4 のミスセンス変異の機能的意義も不明であったので、これらの 3 つの蛋白の以上がなぜ同じ病態を引き起こすのかを明らかにすることで、高血圧症発症の新たな分子メカニズムが明らかとなると考え解明した。その結果、以下の図に示すように、KLHL3-Cullin3 は WNK4 の E3 ユビキチンリガーゼとして機能し、PHAII を引き起こす各々の分子の変異は、採取的に WNK4 の分解を阻害し、その結果増えた WNK4 が下流の OSR1/SPAK キナーゼを活性かする事が PHAIIN の共通の病態である事を世界で初めて明らかにした [1]。



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