Interaction of Angiotensin II Type 1 and D₅ Dopamine Receptors in Renal Proximal Tubule Cells

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Abstract—Angiotensin II type 1 (AT₁) receptor and D₁ and D₁ dopamine receptors directly interact in renal proximal tubule (RPT) cells from normotensive Wistar-Kyoto rats (WKY). There is indirect evidence for a D₅ and AT₁ receptor interaction in WKY and spontaneously hypertensive rats (SHR). Therefore, we sought direct evidence of an interaction between AT₁ and D₅ receptors in RPT cells. D₁ and AT₁ receptors colocalized in WKY cells. Angiotensin II decreased D₅ receptors in WKY cells in a time- and concentration-dependent manner (EC₅₀=2.7×10⁻⁹ M; t₁/₂=4.9 hours), effects that were blocked by an AT₁ receptor antagonist (losartan). In SHR, angiotensin II (10⁻⁸ M/24 hours) also decreased D₅ receptors (0.96±0.08 versus 0.72±0.08; n=12) and to the same degree as in WKY cells (1.44±0.07 versus 0.92±0.08). However, basal D₅ receptors were decreased in SHR RPT cells (SHR 0.96±0.08; WKY 1.44±0.07; n=12 per strain; P<0.05) and renal brush border membranes of SHR compared with WKY (SHR 0.54±0.16 versus WKY 1.46±0.10; n=5 per strain; P<0.05). Angiotensin II decreased AT₁ receptor expression in WKY (1.00±0.04 versus 0.72±0.08; n=8; P<0.05) but increased it in SHR (0.96±0.04 versus 1.32±0.08; n=8; P<0.05). AT₁ and D₅ receptors also interacted in vivo; renal D₅ receptor protein was higher in mice lacking the AT₁ receptor (AT₁⁻/⁻; 1.61±0.31; n=6) than in wild-type littermates used as controls (AT₁⁺/+; 0.81±0.08; n=6; P<0.05), and renal cortical AT₁ receptor protein was higher in D₅ receptor null mice than in wild-type littermates (1.18±0.08 versus 0.84±0.07; n=4; P<0.05). We conclude that D₁ and AT₁ receptors interact with each other. Altered interactions between AT₁ and dopamine receptors may play a role in the pathogenesis of hypertension. (Hypertension. 2005;45[part 2]:804-810.)

Key Words: receptors, dopamine ▶ receptors, angiotensin II ▶ rats, spontaneously hypertensive ▶ normotension ▶ kidney

Several cardiovascular diseases, including hypertension, are associated with abnormal regulation of sodium balance. This balance is regulated by natriuretic and antinatriuretic hormones and humoral agents. Among the numerous factors involved in this process are angiotensin II and dopamine. During moderate volume expansion, renal dopamine production is increased, and dopamine, via D₁-like (comprised of D₁, and D₂ subtypes) and D₂-like receptors (comprised of D₂, D₃, and D₄ subtypes), acts to increase sodium excretion. In contrast, during salt deprivation, angiotensin II production is increased, and angiotensin II, via angiotensin II type 1 (AT₁) receptors, increases renal sodium transport. Angiotensin II antagonizes the natriuretic response elicited by dopamine, and dopamine opposes angiotensin II-mediated sodium transport in the renal proximal tubules (RPTs). Even a small increase in intracellular sodium concentration induces an increase in D₁ receptors and a decrease in AT₁ receptors in renal cell surface membranes. Although the counter-regulation between dopamine and angiotensin II receptors has been shown primarily in RPTs, these receptors may also interact in other areas in the kidney.

In addition to counter-regulation of sodium transport by D₁-like and AT₁ receptors in RPT cells, they also each interact to regulate expression of the other. Activation of D₁-like or D₅ receptors decreases AT₁ receptor expression in RPT cells from normotensive Wistar-Kyoto rats (WKY). Activation of D₁-like or D₅ receptors decreases AT₁ receptor expression in RPT cells from WKY. A physical interaction between the other D₁-like receptor (ie, D₅) and the AT₁ receptor has not been reported, although there is indirect evidence for a negative interaction between D₅ and AT₁ receptors in RPT cells. In that study, we found that a D₅-like receptor, presumably the D₅ receptor, was capable of decreases...
ing AT₁ receptor expression in RPT cells from WKY and spontaneously hypertensive rats (SHR). Therefore, we sought direct evidence of an interaction between the AT₁ receptor and the D₅ receptor in RPT cells and determined whether this interaction is different between WKY and SHR.

Methods

AT₁ Receptor–Deficient Mice

The characteristics and genotyping of mice lacking the AT₁ receptor (AT₁Δ/–) have been reported. The current studies used second-generation AT₁Δ/– mice from first-generation heterozygous mice of mixed C57BL/6 and B129 background from the University of Virginia. Gender-matched, wild-type littermates were stored at centrifuged at 16 000 g for 30 minutes. The supernatants were used as controls (AT₁Δ+/+). After mice were anesthetized with CO₂, kidneys were harvested, snap-frozen in liquid nitrogen, stored at −70°C, and shipped to Georgetown University Medical Center.

Generation of Mice Lacking the D₅ Receptor

The generation of mice lacking the D₅ receptor (D₅/–) has been reported. These mice developed hypertension after 2 months of age. The current studies used D₅/– mice generated in a C57BL/6 Taconic background. Gender-matched, nontransgenic littermates were used as controls (D₅+/+).

Blood Pressure Studies

The rats (Taconic; Germantown, NY) were anesthetized with pentobarbital (50 mg/kg IP) and placed on a heated board to maintain body temperature at 37°C. Catheters were inserted into the femoral vessels and right jugular vein. After stable blood pressures were obtained for ≈30 minutes (verifying that the SHR were hypertensive and the WKY were normotensive), kidneys were removed and the rats euthanized (pentobarbital; 100 mg/kg IV). The renal cortices were homogenized in ice-cold lysis buffer (PBS with 1% Nonidet P-40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate, 1 mmol/L EDTA, 1 mmol/L EGTA, 1 mmol/L PMSF, 10 µg/mL aprotinin, and 10 µg/mL leupeptin), sonicated, kept on ice for 1 hour, and centrifuged at 16 000 g for 30 minutes. The supernatants were stored at −70°C until use for immunoblotting. All experiments were approved by the Georgetown University animal care committee.

Cell Culture

Immortalized RPT cells obtained from 4- to 8-week-old WKY and SHR were cultured at 37°C in 95% air/5% CO₂ atmosphere in DMEM/F-12 culture media. These RPT cells have characteristics similar to freshly obtained RPT brush border membranes and RPTs, at least with regard to D₁ receptors and responses to G-protein stimulation. The cells (80% confluence) were exposed to angiotensin II (10⁻⁸ M) or an AT 1 receptor antagonist losartan. Consistent with the study shown in Figure 1A and 1B, angiotensin II (10⁻⁸ M) decreased D₅ receptors in WKY cells (control 1.10 ± 0.16 versus D₅ receptor expression studied concurrently in RPT cells from SHR and WKY

Confocal Microscopy of Double-Stained RPT Cells

RPT cells, grown on coverslips, were fixed and permeabilized with 100% methanol (30 minutes). The D₅ receptor was visualized using a rabbit anti-human D₅ receptor antibody followed by a fluorescein isothiocyanate (FITC)–conjugated anti-rabbit secondary antibody (Molecular Probes) or by a mouse anti-AT₁ receptor monoclonal antibody (Abcam Limited), followed by an Alexa Fluor 568–goat anti-mouse IgG antibody (Molecular Probes). Cells on coverslips were mounted with the ProLong Antifade Kit (Molecular Probes). Negative controls included absence of primary or secondary antibodies. Immunofluorescence densities and images were acquired (Olympus AX70) at an excitation wavelength of 488 and 568 nm; emission was detected at 535 and 645 nm.

Statistical Analysis

Data are expressed as mean ± SEM. Comparison within groups was made by ANOVA for repeated measures (or paired t test when only 2 groups were compared), and comparison among groups (or t test when only 2 groups were compared) was made by ANOVA with Holm–Sidák test. A value of P<0.05 was considered significant.

Results

AT₁ Receptors Decrease D₅ Receptor Expression in RPT Cells From SHR and WKY

Angiotensin II decreased D₅ receptors in a concentration- and time-dependent manner in RPT cells from WKY. The maximum inhibitory effect was 43%; it was significant at and >10⁻⁸ M; the concentration for half-maximal inhibition was 2.7×10⁻⁸ M (Figure 1A). The inhibitory effect of angiotensin II (10⁻⁸ M) was noted as early as 8 hours and maintained for ≥30 hours (t₁/₂=4.9 hours; Figure 1B).

The specificity of angiotensin II as an AT₁ receptor agonist was also determined by studying the effect of the AT₁ receptor antagonist losartan. Consistent with the study shown in Figure 1A and 1B, angiotensin II (10⁻⁸ M/24 hours), decreased D₅ receptors in WKY cells (control 1.10±0.06; angiotensin II 0.76±0.06; n=7; P<0.05). The AT₁ receptor antagonist losartan (10⁻⁸ M/24 hours), by itself, had no effect on D₅ receptor expression (1.04±0.06) but reversed the inhibitory effect of angiotensin II on D₅ receptor expression (1.10±0.06; Figure 1C).

We next compared the effect of angiotensin II on D₅ receptor expression studied concurrently in RPT cells from WKY and SHR. In RPT cells from WKY and SHR, angiotensin II (10⁻⁸ M/24 hours) also decreased D₅ expression (WKY 1.44±0.07 versus SHR 0.96±0.08 versus 0.72±0.08; n=12), and the degree of reduction in SHR (28±7%) was similar to that noted in WKY cells (35±6%; Figure 1D).

Basal D₅ receptor levels were lower in SHR than in WKY RPT cells (0.96±0.08 versus 1.44±0.07; n=12; Figure 1D). D₅ receptor protein was also decreased in brush border membranes from the kidney of SHR compared with WKY (WKY 1.46±0.16 versus SHR 0.54±0.10; n=5; P<0.01; Figure 1E).

Angiotensin II Decreases AT₁ Receptor Expression in RPT Cells From WKY But Increases It in SHR

To confirm our previous report on the effect of angiotensin II on AT₁ receptor expression in RPT cells, we used a different monoclonal AT₁ antibody in this study. RPT cells were incubated with angiotensin II for the indicated times and
concentrations. Angiotensin II decreased AT1 receptor expression in a concentration- and time-dependent manner in RPT cells from WKY (EC50/EC100 6.6/100 10^8 M; t1/2/EC100 4.2 hours; Figure 2A and 2B). Whereas angiotensin II decreased its own receptor expression in RPT cells from WKY, it increased it in RPT cells from SHR (WKY 1.00/EC100 0.04 versus 0.72/EC100 0.08; SHR 0.96/EC100 0.04 versus 1.32/EC100 0.08; n=8; P<0.05; Figure 2C), in agreement with our previous report.16

**AT1 Receptor Colocalizes With the D5 Receptor in Rat RPT Cells**

To determine the potential for a direct or indirect interaction between D5 and AT1 receptors, we studied the colocalization of D5 and AT1 receptors in RPT cells from WKY. D5 and AT1 receptors were found throughout the cell, with evidence of colocalization, especially at the cell surface membrane (Figure 3). To determine whether there is a physical interaction

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**Figure 1.** Effect of angiotensin II on D5 receptor protein expression in RPT cells from WKY and SHR. A, Concentration response of D5 receptor expression in RPT cells from WKY treated with angiotensin II. Immunoreactive D5 receptor expression was determined after 24-hour incubation with the indicated concentrations of angiotensin II. Results are expressed as relative density units (DU; n=7; *P<0.05 vs control [C]; ANOVA; Holm–Sidak test). B, Time course of D5 receptor expression in RPT cells from WKY treated with angiotensin II. Cells were incubated for the indicated times with 10^-8 M angiotensin II. Results are expressed as relative DU (n=7; *P<0.05 vs control [0 time]; ANOVA; Holm–Sidak test). C, Effect of angiotensin II (Ang II) and an AT1 receptor antagonist (losartan) on D5 receptor expression in RPT cells from WKY. Cells were incubated with the indicated reagents, respectively (Ang II 10^-8 M; losartan 10^-8 M), for 24 hours. Results are expressed as the ratio of D5 receptor to α-actin densities (n=7; *P<0.05 vs others; ANOVA; Holm–Sidak test). D, Effect of angiotensin (10^-8 M/24 hours) on D5 receptor expression in RPT cells from WKY and SHR. Results are expressed as the ratio of D5 receptor to α-actin densities (n=12; *P<0.05; control; *P<0.05 vs WKY; ANOVA; Holm–Sidak test). E, Immunoreactive D5 receptor in renal brush border membranes of WKY and SHR. Results are expressed as the ratio of D5 receptor to α-actin densities (n=5; *P<0.01 vs WKY; t test).

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**Figure 2.** Effect of angiotensin II on AT1 receptor expression in RPT cells from WKY and SHR. A, Concentration response of AT1 receptor expression in rat RPT cells from WKY treated with angiotensin II. Immunoreactive AT1 receptor expression was determined after 24-hour incubation with the indicated concentrations of angiotensin II. Results are expressed as relative density units (DU; n=11; *P<0.05 vs control; ANOVA; Holm–Sidak test). B, Time course of AT1 receptor expression in RPT cells from WKY treated with angiotensin II. Cells were incubated for the indicated times with 10^-8 M angiotensin II. Results are expressed as relative DU (n=11; *P<0.05 vs control [0 time]; ANOVA; Holm–Sidak test). C, Effect of angiotensin (10^-8 M/24 hours) on AT1 receptor expression in RPT cells from WKY and SHR. Results are expressed as the ratio of AT1 receptor to α-actin densities (n=5; *P<0.05; control; ANOVA; Holm–Sidak test).
D₅ Receptor AT₁ Receptor Merge

Figure 3. D₅ and AT₁ receptor colocalization in RPT cells from WKY. Cells were washed, fixed, and immunostained for D₅ and AT₁ receptors, as described in the Methods. Colocalization appears as yellow after merging the images of FITC-tagged D₅ receptor (green) and Alexa 568-tagged AT₁ receptor (red).

between the D₅ and the AT₁ receptor, additional experiments were performed. D₅ receptors were first immunoprecipitated with anti-D₅ receptor antibodies and the immunoprecipitate analyzed by immunoblotting with anti-AT₁ receptor antibodies. Additionally, antibodies were reversed for immunoprecipitation and immunoblotting. No D₅/AT₁ receptor coimmunoprecipitation bands were found (data not shown).

D₅ Receptor Expression Is Increased in the Kidneys of AT₁⁻/⁻ Mice

Although the coimmunoprecipitation study showed no evidence for a direct physical interaction between AT₁ and D₅ receptors, we determined whether the AT₁ receptor could regulate D₅ receptor expression in vivo. The D₅ and AT₁ receptors each can regulate expression of the other because D₅ receptor protein expression was greater in kidneys of AT₁⁻/⁻ (1.61 ± 0.31; n = 6) than AT₁⁺/+ littermates (0.81 ± 0.08; n = 6; P < 0.05; Figure 4).

AT₁ Receptor Expression Is Increased in the Kidneys of D₅⁻/⁻ Mice

We next determined whether the D₅ receptor could regulate AT₁ receptor expression in vivo. We found that F₆ pentobarbital-anesthetized congenic D₅⁻/⁻ mice (F₆) had higher systolic blood pressure (SBP) and diastolic blood pressure (DBP; SBP 117 ± 5 mm Hg; DBP 85 ± 2 mm Hg; n = 5) than wild-type C57BL/6 (Taconic) mice (SBP 94 ± 2 mm Hg; DBP 69 ± 3 mm Hg; n = 5; P < 0.05; t test), in agreement with previous reports.²³,³¹ The arterial blood pressures of awake D₅⁻/⁻ mice were in the hypertensive range.²³,³¹ Immunoreactive AT₁ receptors were also greater in the kidney of D₅⁻/⁻ than D₅⁺/+ littermates (D₅⁻/⁻ 1.18 ± 0.08; D₅⁺/+ 0.84 ± 0.07; n = 4; P < 0.05; Figure 5).

Discussion

Alterations in the responsiveness of the proximal tubule to angiotensin II and dopamine have important implications for net sodium reabsorption. Several studies have shown that the dopaminergic and renin-angiotensin systems interact to regulate renal function.⁹,¹¹,¹⁶ For example, inhibition of renal angiotensin II production or blockade of AT₁ receptors increases the natriuretic effect of the D₁-like agonist fenoldopam.⁹,¹² D₁-like and D₂-like receptor agonists also antagonize the stimulatory effect of angiotensin II, acting via AT₁ receptors, on renal proximal tubular luminal sodium transport.¹⁰,³³,³⁴ The renal vasoconstrictor effect of angiotensin II can also be antagonized by D₁-like receptor agonists.¹⁵ and angiotensin-converting enzyme inhibition augments the renal vasoconstrictor effect of a D₅-like receptor agonist.³⁶ Our previous studies showed that dopamine, via D₁-like and D₃ receptors, inhibits AT₁ receptor expression.¹⁵,¹⁷ Indirect evidence suggests that the D₃ receptor may be involved in the inhibitory effects of a D₅-like receptor on AT₁ receptor.¹⁵ This is consistent with our finding in human RPT cells indicating that the D₅ but not the D₃ receptor decreases AT₁ receptor expression,³⁷ and AT₁ receptor expression in renal cortical membrane of D₅⁻/⁻ mice is increased relative to wild-type littermates.

To better understand the interaction between dopamine and AT₁ receptors, we investigated the effect of AT₁ receptor activation on the expression of dopamine receptor subtypes in RPT cells. In a preliminary communication, we reported that...
activation of the AT$_1$ receptor increases D$_5$ receptor expression in RPT cells from WKY but not from SHR.\textsuperscript{18}

The ability of dopamine and D$_1$-like agonists to couple to signal transducers and decrease renal proximal tubular sodium reabsorption is impaired in genetic rodent hypertension and human essential hypertension.\textsuperscript{1,5,7,8,26,38} Indeed, the aberrant D$_1$-like receptor function in the kidney precedes and cosegregates with high blood pressure in SHR.\textsuperscript{1,5,7,8} In addition, disruption of the D$_5$ or D$_7$ receptor in mice produces hypertension.\textsuperscript{23,31,39} Although total cellular D$_1$ receptor expression is not different in RPT cells of WKY and SHR, D$_1$-like receptor-mediated natriuresis is impaired in SHR because of an uncoupling of D$_1$-like receptors from their G-protein effector enzyme complex.\textsuperscript{1,5,7,8,26} In this study, we find that D$_5$ receptor expression is decreased in RPT cell and renal brush border membranes from SHR compared with WKY cells. Because the increase in cAMP levels after D$_1$-like receptor stimulation is attributable mainly to the D$_1$ receptor relative to the D$_5$ receptor,\textsuperscript{40} we speculate that the effect of AT$_1$ receptors on D$_5$ receptor expression may not have as significant an impact on renal tubular function relative to the effect of the AT$_1$ receptor on the D$_1$ receptor. However, the ability of the D$_5$ receptor to negatively regulate the AT$_1$ receptor may have a significant impact on the regulation of blood pressure. Indeed, in the current report, we show that renal D$_5$ receptor protein is increased in AT$_1$-deficient mice, and renal AT$_1$ receptor is increased in D$_5$ receptor-deficient mice, relative to their wild-type littermates.

The role of this differential expression of D$_5$ receptors on renal sodium handling remains to be determined. However, the hypertension in D$_5^{-/-}$ mice is aggravated by increased sodium intake.\textsuperscript{41} We speculate that this may be, in part, attributable to increased renal expression of AT$_1$ receptors. We have preliminary studies showing that the intraperitoneal administration of the AT$_1$ receptor antagonist losartan (20 mg/kg per day for 8 days) normalized blood pressure in pentobarbital D$_5^{-/-}$ mice but minimally affected blood pressure in D$_5$ +/- littermates (L.D. Asico et al, unpublished data, 2004). The decreased expression of D$_5$ receptors in SHR and the increased expression of AT$_1$ receptors in D$_5^{-/-}$ mice may be a mechanism of the unmitigated AT$_1$ receptor function in hypertension.

The mechanism for the decrease in D$_5$ receptor caused by AT$_1$ receptors was not studied. We find colocalization of D$_1$ and AT$_1$ receptors in RPT cells. However, there is no physical interaction determined by coimmunoprecipitation study, which indicates that D$_5$ and AT$_1$ receptors interact with each other via an indirect pathway. We have reported in a preliminary communication that the D$_5$ receptor decreases AT$_1$ receptor expression by increasing its degradation in human RPT cells.\textsuperscript{37} It is possible that the AT$_1$ receptor regulates D$_5$ receptor expression by similar mechanisms.

The effect of angiotensin II on AT$_1$ receptor expression in RPT cells has not been consistent. In rabbit RPT cells, a 16-hour incubation with angiotensin II dose-dependently increases AT$_1$ receptor expression, assessed by radioligand binding.\textsuperscript{42} AT$_1$ receptor mRNAs in rat and rabbit RPT cells are also increased by angiotensin II.\textsuperscript{43,44} However, the intravenous administration of angiotensin II that increases systemic blood pressure does not alter immunoreactive renal AT$_1$ receptor expression but decreases AT$_1$ receptor expression (radioligand autoradiography) in glomeruli and inner stripe of the outer medulla. Three days after the infusion of angiotensin II, there is a tendency for a decrease in AT$_1$ expression in the whole kidney and in RPTs, but the changes are modest and do not reach statistical significance.\textsuperscript{44} We reported that angiotensin II decreases AT$_1$ receptor, determined by immunoblotting, in cells from WKY.\textsuperscript{16} Because the specificity of commercially available antibodies has been questioned, the current studies used a different AT$_1$ receptor antibody. Using a monoclonal AT$_1$ receptor antibody, we again find that angiotensin II decreases AT$_1$ expression in RPT cells from WKY but produces the opposite effect in SHR. This contrasting effect of angiotensin II on AT$_1$ receptor expression in WKY and SHR suggests that our findings cannot be explained by limitations of AT$_1$ receptor antibodies. Rather, the strain-specific effect of angiotensin II on AT$_1$ receptor may be important in the pathogenesis of hypertension in SHR. However, it is realized that the renal expression of AT$_1$ receptors in SHR has not been consistently shown to be elevated.\textsuperscript{45--52} For example, ovariectomy or salt loading in SHR increases renal AT$_1$ receptors.\textsuperscript{44,45} However, renal outer medullary but not cortical AT$_1$ expression has been reported to be increased in SHR relative to WKY.\textsuperscript{47,48} An autoradiographic study showed increased angiotensin II binding in all areas of the kidney of SHR (relative to WKY) at 1 week of age.\textsuperscript{49} Renal cortical and brush border membrane AT$_1$ receptor binding is also higher in 4-week-old SHR relative to WKY.\textsuperscript{50} AT$_1$ receptor expression is higher in certain cerebral nuclei and arteries of adult SHR relative to WKY.\textsuperscript{51,52} We also find no difference in AT$_1$ receptor protein in RPT cells from WKY and SHR. In contrast, AT$_1$ receptor expression in brush border membranes is higher in SHR than in WKY.\textsuperscript{53} It is possible that discrepancies in published studies may be related to differences in membrane preparation.

In summary, we have demonstrated that activation (constitutively or via their respective ligands) of D$_5$ and AT$_1$ receptors negatively regulates the expression of each other. Taken together with our previous studies on the negative interaction between D$_5$/D$_7$ receptors on the one hand and AT$_1$ receptors on the other, dopamine receptors and AT$_1$ receptors may counter-regulate each other. Such a counter-regulation may have important implications in the regulation of sodium excretion and blood pressure.

Perspectives

Dopamine, mainly via D$_1$-like receptor (D$_1$ and D$_7$), increases sodium excretion by inhibition of NHE3, Na$^+$/K$^+$ ATPase, Cl$^-$/HCO$_3^-$, and Na$^+$/HCO$_3^-$ exchanger activities. Conversely, angiotensin II, via AT$_1$ receptor, decreases sodium excretion by stimulation of renal tubular ion transport.\textsuperscript{1--8} Whereas there is reciprocal dopamine and angiotensin modulation in WKY, this effect is altered in SHR. The faulty D$_5$ receptor cannot counter the effects of AT$_1$ receptors in SHR, and the negative modulating action of angiotensin II on AT$_1$ receptors in WKY is actually reversed in SHR. The net result is enhanced antinatriuresis. Although the D$_3$ receptor contin-
ues to be a negative regulator of AT1r in SHR, the decreased expression of D5 receptors compared with WKYs may limit its effectiveness. Transregulation at the protein level, by alterations in protein synthesis or degradation, is a mechanism by which these receptors regulate each other.

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