Dopamine D1 Receptor Regulation of Phospholipase C

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Dopamine is an endogenous catecholamine which exerts its actions by occupancy of specific receptors. Dopamine receptors are classified into two main groups: the two cloned D1-like receptors (D1A and D1B in rats; D1B is also known as D5 in humans) are linked to stimulation of adenylyl cyclase, while the three cloned D2-like receptors (D2 or D2A, D3 or D2B, D4 or D2C) are linked to inhibition of adenylyl cyclase. All these dopamine receptors originally cloned from the brain are expressed in tissues outside the central nervous system including the kidney. Dopamine regulates many cellular activities, including transmembrane ion transport. Activation of D1-like receptor decreases sodium transport by cAMP dependent and cAMP independent mechanisms. Dopamine, via D1-like receptors, may inhibit Na+/H+ exchange activity in renal brush border membranes by a cAMP independent/Gs-Linked mechanism. Another cAMP independent pathway of sodium transport inhibition is mediated by phospholipase C, which has several isoforms (PLCβ, PLCγ, and PLCδ with several members in each). Catecholamines stimulate expression and activity of phospholipase C isoforms in a concentration, time, and receptor-dependent as well as regional and subcellular compartmental-specific manner. In renal cortical membranes, intrarenal administration of norepinephrine for 3-4 h increases PLCβ expression and activity but has no effect on PLCγ activity. In contrast, intrarenal administration of a D1 agonist for 3-4 h increases PLCβ but decreases PLCγ expression and activity. In membranes from LTK - cells transfected with the rat D1A receptor cDNA, D1 receptor stimulation initially increases and then in 4 h decreases PLCγ expression and activity, similar to the results found in renal cortical membranes. The initial increase of PLCγ expression and activity due to D1 receptors is mediated by protein kinase A. (Hypertens Res 1995; 18 Suppl. I: S39–S42)

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transport inhibition is mediated by phospholipase C (16-18). The stimulatory effect of dopamine on phospholipase C activity, initially reported in renal cortical membranes, has been demonstrated in specific areas of the brain and in the retina (23-29). In the kidney, dopamine-mediated stimulation of phospholipase C activity is exerted via a D₁-like receptor since the stimulatory effect is blocked by "D₁" antagonists like SCH 23390 and stimulated by "D₁" agonists like fenoldopam and SKF 38393 (23). Furthermore, a pertussis toxin resistant G-protein was found to be linked to the D₁-like receptor-stimulated phospholipase C activity (24). In the kidney, inhibition of phospholipase C activity does not after the inhibitory effect of dopamine agonists on Na⁺/K⁺ exchange activity in renal brush border membranes (30) but does prevent their inhibitory effect on Na⁺/K⁺ ATPase activity (18). Indeed, the natriuresis of sodium loading due to dopamine has been attributed to a dopamine-mediated stimulation of phospholipase C activity (31).

Several phospholipase C enzymes have been purified, molecularly cloned and sequenced (32, 33). These isoforms of phospholipase C have been grouped into three families, PLCβ, PLCγ, and PLCδ with several members in each (e.g. PLCβ₁, PLCβ₂, PLCβ₃). Phospholipase C has been linked to pertussis toxin sensitive and insensitive G proteins and tyrosine kinases (33-37). The Gq family of G proteins, which are pertussis toxin insensitive, have been linked to activation of PLCβ₁ while tyrosine kinases activate PLCγ₁. In reconstituted systems, several receptors have been reported to activate phospholipase C via Gq including thromboxane A₂, bradykinin, angiotensin II, histamine, vasopressin, acetylcholine muscarinic (M₁, M₃, M₅), α₁-adrenergic (α₁A, α₁C), α₂-adrenergic (α₂), and serotonergic (5-HT₁c) receptors (38). PLCβ isoforms (PLCβ₁ > PLCβ₂ > PLCβ₃) can also be activated by G-protein βγ subunits independently of α-subunits (39). We recently reported the linkage of dopamine and ß-adrenergic receptors to phospholipase C isoforms in renal cortical tissue (40). We found that a 3-4 h intravenous or intrarenal arterial infusion of norepinephrine or a D₁ agonist which produces an antinatriuresis and natriuresis, respectively, increases PLCβ₁ expression and activity in renal cortical membranes like the other Gq-protein linked receptors (38, 40). We also found that G-protein linked receptors alter the expression and activity PLCγ₁ (40) confirming an earlier report that G-protein linked receptors can affect PLCγ activity (41). Thus, we reported that a 3-4 h intravenous or intrarenal arterial infusion of two chemically unrelated dopamine receptor agonists, the D₁ agonist fenoldopam and the D₁/D₂/D₃ receptor agonist pramipexole, decreases PLCγ expression and activity in the membrane. In contrast, 3-4 h intrarenal arterial infusion of norepinephrine increases PLCβ₁ expression and activity but does not affect PLCγ activity in the membrane. These actions of dopaminergic agonists do not occur in medullary membranes. Furthermore, there are no effects of dopamine agonists on PLCδ in either cortex or medulla.
The putative D1 receptor linked to phospholipase C stimulation is yet to be cloned. Initial studies with the cloned D1-like receptors (D1A and D1B) failed to show linkage with phospholipase C. Recently, one of the D1 receptors linked to stimulation of adenyl cyclase (D1A) was also found to stimulate phosphoinositide hydrolysis via cholera toxin sensitive G-proteins in murine fibroblasts (LTK- cells) transfected with the human or rat D1A receptor cDNA (42). In preliminary studies, we also found that the D1 agonist, fenoldopam, stimulates phospholipase C activity in LTK- cells transfected with the rat D1A receptor cDNA in a concentration and time dependent manner (43). In LTK- cells where PLCβ1 is minimally expressed, fenoldopam initially (<60 min) stimulates PLCγ expression in cytosol and membrane. However, 4 h of fenoldopam stimulation decreases PLCγ expression below basal levels in membranes while PLCγ expression remains elevated in the cytosol, similar to the findings in renal cortical tissue. The initial ability of fenoldopam to stimulate PLCγ expression in the membrane is mimicked by forskolin and the protein kinase A agonist, Sp-cAMPS, and is blocked by the protein kinase A inhibitor, Rp-cAMPS, indicating involvement of protein kinase A in this action. Protein kinase C is also involved since phorbol myristate acetate, which stimulates protein kinase C, stimulates PLCγ expression. Furthermore, protein kinase C blockers prevent the initial stimulatory effect of fenoldopam and forskolin on PLCγ expression in membranes while fenoldopam and forskolin stimulate protein kinase Ca expression. Moreover, forskolin and Sp-cAMPS stimulate protein kinase C activity. Glucagon, calcitonin, forskolin, and cAMP analogues 8-Br-cAMP and 8CPT-cAMP have also been reported to stimulate phosphatidylinositol 1, 4, 5 trisphosphate production in hepatocytes and skeletal muscle cells (44, 45). Thus, the initial stimulatory effect of fenoldopam on PLCγ expression in membranes from LTK- cells heterologously expressing D1A receptors is likely to be mediated by a stimulatory effect of protein kinase A on protein kinase C.

In summary, in the kidney, catecholamines stimulate the expression and activity of phospholipase C isoforms in a concentration, time and receptor dependent manner. In addition, phospholipase C regulation is regional and subcellular compartment-specific. Three to four hour stimulation of noradrenaline increases PLCβ expression and activity but has no effect on PLCγ activity in renal cortical membranes. There to 4 h stimulation by D1 agonists also increases PLCβ1 expression and activity in membranes but decreases expression and activity of PLCγ1 in membranes from renal cortex and LTK- cells heterologously expressing the rat D1A receptor. No changes in phospholipase C isoforms are noted in the renal medulla. PLCδ expression is not affected by D1 agonists in either cortex or medulla. In LTK- cells, where PLCβ1 is negligibly expressed, transfection with the rat D1A cDNA results in functional expression of the receptor with linkage to both adenyl cyclase and phospholipase C stimulation. The stimulatory effect of D1 agonists in these transfected cells occurs early in both cytosol and membranes. However, 4 h of D1 receptor stimulation decreases expression of PLCγ1 in membranes while expression in cytosol remains elevated as in the renal cortical studies. The short-term increase in PLCγ1 expression in these transfected cells, induced by occupancy of D1A receptors, is mediated by protein kinase A stimulation of protein kinase C activity.

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