Tyrosine Hydroxylase Phosphorylation

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Tyrosine hydroxylase (TH) is the rate-limiting enzyme of dopamine biosynthesis. The phosphorylation of TH is strictly regulated.

Keywords: tyrosine hydroxylase ; phosphorylation ; dephosphorylation ; cAMP-dependent protein kinase ; protein phosphatase 2A ; dopamine ; ubiquitin-proteasome system

1.Introduction

TH is activated by phosphorylation by a cAMP-dependent protein kinase and deactivated by dephosphorylation by protein phosphatase 2A. The dysregulation of TH phosphorylation leads to its aggregation or degradation by the ubiquitin-proteasome system, presumably associated with the etiology of Parkinson's disease and dopa-responsive dystonia.

2.Physiology

Tyrosine hydroxylase (TH) is a rate-limiting enzyme for dopamine biosynthesis [1] and is selectively expressed in monoaminergic neurons in the central nervous system. In humans, TH protein has four isoforms with different molecular weight, which are derived from the same gene through alternative splicing of mRNA [2][3]. This protein also has two isoforms in monkeys and only a single isoform in all nonprimate mammals [4][5]. The catalytic domain of TH is located within the C-terminal area, whereas the region that controls enzyme activity (the regulatory domain) is located at the N-terminal end [6]. Four phosphorylation sites, namely Ser8, Ser19, Ser31, and Ser40, have been identified in the N-terminal region of TH [7], whereas the catalytic domain is in 188–456 amino acid residue [8]. TH is a homotetramer consisting of four subunits, and the C-terminal domain forms this homotetramer structure [9]. The phosphorylation of TH is strictly regulated [10][11]. The dysregulation leads to its aggregation [12][13] or degradation by the ubiquitin-proteasome system [14] [15].

Two mechanisms can modulate the activity of TH: one is a medium- to long-term regulation of gene expression, such as enzyme stability, transcriptional regulation, RNA stability, alternative RNA splicing, and translational regulation. The regulation of TH is well known; its expression level depends on transcription driven by cyclic adenosine monophosphate (cAMP)-dependent responsive element (in promoter) [16] in a manner dependent on activator protein 1 (AP-1) [17][18], serum-responsive factor (SRF) [19], and nuclear receptor related-1 (Nurr1) [20]. The other is a short-term regulation of enzyme activity, such as feedback inhibition, allosteric regulation, and phosphorylation [16][10][11]. Many factors strictly regulate the activity of TH to control dopamine biosynthesis. Upon depolarization, cyclic AMP-dependent protein kinase (PKA) and calcium-calmodulin-dependent protein kinase II (CaMKII) are activated [21][22][23]. PKA phosphorylates TH at Ser40 and CaMKII phosphorylates TH at Ser19 [24][25]. Phosphorylation of Ser19 increases Ser40 phosphorylation, indicating that the phosphorylation of Ser19 can potentiate the phosphorylation of Ser40 and subsequent activation of TH [26]. Other stress-related protein kinases can also phosphorylate TH at Ser40 [10][11]. Phosphorylation at Ser40 leads to the liberation of dopamine from the active site of TH and changes the conformation to the high specific activity form [27]. Cytosolic free dopamine can bind to the active site of TH and deactivate the enzyme to suppress dopamine overproduction [28][29]. It has been reported that the phosphorylated form of TH is highly labile, whereas the dopamine-bound form is stable [30]. TH phosphorylated at Ser40 (pSer40-TH) is dephosphorylated by a protein phosphatase, such as protein phosphatase 2A (PP2A), because inhibition of PP2A with okadaic acid or microcystin induces an increase in pSer40-TH level [31][32][33]. Ser31 phosphorylation is mediated by extracellular signal-regulated kinase 1 (ERK1) and ERK2 [5][34], and its dephosphorylation is mediated by PP2A [33]. Because ERK signals are usually activated as part of the mitogen-activated protein kinase (MAPK) cascade for cell survival, dephosphorylation of TH phosphorylated at Ser31 (pSer31-TH) is very rare in living cells. Phosphorylation of TH at Ser8 has been shown in cultured rat pheochromocytoma

PC12 cells and permeabilized bovine chromaffin cells after treatment with okadaic acid [24][33]. In contrast, no significant phenomena have been reported in cultured dopaminergic neurons and *in vivo*. These data suggest that TH regulation by Ser8 phosphorylation is not critical in the central nervous system.

References

1. T Nagatsu; M Levitt; S Udenfriend; Tyrosine Hydroxylase. The initial step in norepinephrine biosynthesis.. *Journal of Biological Chemistry* **1964**, *239*, 2910-2917, .
2. Norio Kaneda; Kazuto Kobayashi; Hiroshi Ichinose; Fumio Kishi; Atsushi Nakazawa; Yoshikazu Kurosawa; Keisuke Fujita; Toshiharu Nagatsu; Isolation of a novel cDNA clone for human tyrosine hydroxylase: Alternative RNA splicing produces four kinds of mRNA from a single gene. *Biochemical and Biophysical Research Communications* **1987**, *146*, 971-975, 10.1016/0006-291x(87)90742-x.
3. Brigitte Grima; Annie Lamouroux; Claudette Boni; Jean-François Julien; France Javoy-Agid; Jacques Mallet; A single human gene encoding multiple tyrosine hydroxylases with different predicted functional characteristics. *Nature* **1987**, *326*, 707-711, 10.1038/326707a0.
4. Hiroshi Ichinose; T. Ohye; K. Fujita; M. Yoshida; S. Ueda; T. Nagatsu; Increased Heterogeneity of Tyrosine Hydroxylase in Humans. *Biochemical and Biophysical Research Communications* **1993**, *195*, 158-165, 10.1006/bbrc.1993.2024.
5. John W. Haycock; Species differences in the expression of multiple tyrosine hydroxylase protein isoforms.. *Journal of Neurochemistry* **2002**, *81*, 947-953, 10.1046/j.1471-4159.2002.00881.x.
6. C Abate; T H Joh; Limited proteolysis of rat brain tyrosine hydroxylase defines an N-terminal region required for regulation of cofactor binding and directing substrate specificity.. *Journal of Molecular Neuroscience* **1991**, *2*, 203-215, .
7. D G Campbell; D G Hardie; P R Vulliet; Identification of four phosphorylation sites in the N-terminal region of tyrosine hydroxylase.. *Journal of Biological Chemistry* **1986**, *261*, 10489–10492, .
8. Kenneth E. Goodwill; Christelle Sabatier; Cara Marks; Reetta Raag; Paul F. Fitzpatrick; Raymond C Stevens; Crystal structure of tyrosine hydroxylase at 2.3 A and its implications for inherited neurodegenerative diseases.. *Nature Genetics* **1997**, *4*, 578-585, 10.1038/nsb0797-578.
9. J P Mitchell; D G Hardie; P R Vulliet; Site-specific phosphorylation of tyrosine hydroxylase after KCl depolarization and nerve growth factor treatment of PC12 cells.. *Journal of Biological Chemistry* **1990**, *265*, 22358–22364, .
10. Peter R. Dunkley; Larisa Bobrovskaya; Mark Graham; Ellak I. Von Nagy-Felsobuki; Phillip W. Dickson; Tyrosine hydroxylase phosphorylation: regulation and consequences. *Journal of Neurochemistry* **2004**, *91*, 1025-1043, 10.1111/j.1471-4159.2004.02797.x.
11. Peter R. Dunkley; Phillip W. Dickson; Tyrosine hydroxylase phosphorylation in vivo. *Journal of Neurochemistry* **2019**, *149*, 706-728, 10.1111/jnc.14675.
12. Ichiro Kawahata; Hirofumi Tokuoka; Hasan Parvez; Hiroshi Ichinose; Accumulation of phosphorylated tyrosine hydroxylase into insoluble protein aggregates by inhibition of an ubiquitin–proteasome system in PC12D cells. *Journal of Neural Transmission* **2009**, *116*, 1571-1578, 10.1007/s00702-009-0304-z.
13. Kawahata, I.; Yagishita, S.; Hasegawa, K.; Nagatsu, I.; Nagatsu, T.; Ichinose, H; Immunohistochemical analyses of the postmortem human brains from patients with Parkinson’s disease with anti-tyrosine hydroxylase antibodies. *Biog. Amines* **2009**, *23*, 1-7, .
14. Ichiro Kawahata; Shiori Ohtaku; Yoshihisa Tomioka; Hiroshi Ichinose; Tohru Yamakuni; Dopamine or biopterin deficiency potentiates phosphorylation at 40 Ser and ubiquitination of tyrosine hydroxylase to be degraded by the ubiquitin proteasome system. *Biochemical and Biophysical Research Communications* **2015**, *465*, 53-58, 10.1016/j.bbrc.2015.07.125.
15. Ichiro Kawahata; Kohji Fukunaga; Degradation of Tyrosine Hydroxylase by the Ubiquitin-Proteasome System in the Pathogenesis of Parkinson’s Disease and Dopa-Responsive Dystonia. *International Journal of Molecular Sciences* **2020**, *21*, 3779, 10.3390/ijms21113779.
16. Sean C. Kumer; Kent E. Vrana; Intricate Regulation of Tyrosine Hydroxylase Activity and Gene Expression. *Journal of Neurochemistry* **2002**, *67*, 443-462, 10.1046/j.1471-4159.1996.67020443.x.
17. Hee-Don Chae; Byung-Chang Suh; Tong H. Joh; Kyong-Tai Kim; AP1-Mediated Transcriptional Enhancement of the Rat Tyrosine Hydroxylase Gene by Muscarinic Stimulation. *Journal of Neurochemistry* **2002**, *66*, 1264-1272, 10.1046/j.1471-4159.1996.66031264.x.

18. Zheng Guo; Xinyu Du; Lorraine Iacovitti; Regulation of Tyrosine Hydroxylase Gene Expression during Transdifferentiation of Striatal Neurons: Changes in Transcription Factors Binding the AP-1 Site. *The Journal of Neuroscience* **1998**, *18*, 8163-8174, 10.1523/JNEUROSCI.18-20-08163.1998.

19. Ichiro Kawahata; Y. Lai; J. Morita; S. Kato; S. Ohtaku; Y. Tomioka; A. Tabuchi; M. Tsuda; C. Sumi-Ichinose; K. Kondo; et al. V-1/CP complex formation is required for genetic co-regulation of adult nigrostriatal dopaminergic function via the RHO/MAL/SRF pathway in vitro and in vivo. *Journal of the Neurological Sciences* **2017**, *381*, 359-360, 10.1016/j.jns.2017.08.1021.

20. Banafsheh Kadkhodaei; Takehito Ito; Eliza Joodmardi; Bengt Mattsson; Claude Rouillard; Manolo Carta; Shin-Ichi Muramatsu; Chiho Sumi-Ichinose; Takahide Nomura; Daniel Metzger; et al. Nurr1 Is Required for Maintenance of Maturing and Adult Midbrain Dopamine Neurons. *The Journal of Neuroscience* **2009**, *29*, 15923-15932, 10.1523/JNEUROSCI.3910-09.2009.

21. K Fukunaga; D P Rich; T R Soderling; Generation of the Ca2(+)-independent form of Ca2+/calmodulin-dependent protein kinase II in cerebellar granule cells.. *Journal of Biological Chemistry* **1989**, *264*, 21830–21836, .

22. Kohji Fukunaga; E Miyamoto; T R Soderling; Regulation of Ca2+/calmodulin-dependent protein kinase II by brain gangliosides.. *Journal of Neurochemistry* **1990**, *54*, 103–109, .

23. T R Soderling; K Fukunaga; D P Rich; Y L Fong; K Smith; R J Colbran; Regulation of brain Ca2+/calmodulin-dependent protein kinase II.. *Advances in second messenger and phosphoprotein research* **1990**, *24*, 206–211, .

24. J W Haycock; Phosphorylation of tyrosine hydroxylase in situ at serine 8, 19, 31, and 40.. *Journal of Biological Chemistry* **1990**, *265*, 11682–11691, .

25. J W Haycock; D A Haycock; Tyrosine hydroxylase in rat brain dopaminergic nerve terminals. Multiple-site phosphorylation in vivo and in synaptosomes.. *Journal of Biological Chemistry* **1991**, *266*, 5650–5657, .

26. Larisa Bobrovskaya; Peter R. Dunkley; Phillip W. Dickson; Phosphorylation of Ser19 increases both Ser40 phosphorylation and enzyme activity of tyrosine hydroxylase in intact cells. *Journal of Neurochemistry* **2004**, *90*, 857-864, 10.1111/j.1471-4159.2004.02550.x.

27. S C Daubner; C Lauriano; J W Haycock; P F Fitzpatrick; Site-directed mutagenesis of serine 40 of rat tyrosine hydroxylase. Effects of dopamine and cAMP-dependent phosphorylation on enzyme activity.. *Journal of Biological Chemistry* **1992**, *267*, 12639–12646, .

28. S Okuno; Hitoshi Fujisawa; A new mechanism for regulation of tyrosine 3-monooxygenase by end product and cyclic AMP-dependent protein kinase.. *Journal of Biological Chemistry* **1985**, *260*, 2633–2635, .

29. Hitoshi Fujisawa; Sachiko Okuno; Regulatory mechanism of tyrosine hydroxylase activity. *Biochemical and Biophysical Research Communications* **2005**, *338*, 271-276, 10.1016/j.bbrc.2005.07.183.

30. Montserrat Royo; Paul F. Fitzpatrick; S. Colette Daubner; Mutation of regulatory serines of rat tyrosine hydroxylase to glutamate: effects on enzyme stability and activity. *Archives of Biochemistry and Biophysics* **2005**, *434*, 266-274, 10.1016/j.abb.2004.11.007.

31. J Haavik; D L Schelling; D G Campbell; K K Andersson; T Flatmark; P Cohen; Identification of protein phosphatase 2A as the major tyrosine hydroxylase phosphatase in adrenal medulla and corpus striatum: evidence from the effects of okadaic acid.. *FEBS Letters* **1989**, *251*, 36–42, .

32. C A Gonçalves; A Hall; A T Sim; S J Bunn; P D Marley; T B Cheah; P R Dunkley; Tyrosine hydroxylase phosphorylation in digitonin-permeabilized bovine adrenal chromaffin cells: the effect of protein kinase and phosphatase inhibitors on Ser19 and Ser40 phosphorylation.. *Journal of Neurochemistry* **1997**, *69*, 2387–2396, .

33. Rodrigo Leal; Alistair T. R. Sim; Carlos A. S. Gonçalves; Peter R. Dunkley; Tyrosine hydroxylase dephosphorylation by protein phosphatase 2A in bovine adrenal chromaffin cells.. *Neurochemical Research* **2002**, *27*, 207-213, 10.1023/a:1014880403970.

34. John W Haycock; Peptide substrates for ERK1/2: structure-function studies of serine 31 in tyrosine hydroxylase. *Journal of Neuroscience Methods* **2002**, *116*, 29-34, 10.1016/s0165-0270(02)00025-0.