CHINESE JOURNAL OF PHYSIOLOGY
Official publication of Chinese Physiological Society

ORIGINAL ARTICLE
Year : 2019 | **Volume** : 62 | **Issue** : 2 | **Page** : 63-69

Knockdown of protein kinase CK2 blocked gene expression mediated by brain-derived neurotrophic factor-induced serum response element

Shu-Ping Yang[1], Chi-Yi Lo[1], Hui-Min Tseng[1], Chih-Chang Chao[2]
[1] Institute of Neurosciences, National Chengchi University, Taipei, Taiwan
[2] Institute of Neurosciences, National Chengchi University; Research Center for Mind, Brian and Learning, National Chengchi University, Taipei, Taiwan

Date of Submission	09-Jan-2019
Date of Decision	27-Mar-2019
Date of Acceptance	08-Apr-2019
Date of Web Publication	25-Apr-2019

Correspondence Address:
Dr. Chih-Chang Chao
Institute of Neurosciences, National Chengchi University, Taipei; Research Center for Mind, Brian and Learning, National Chengchi University, Taipei
Taiwan
Login to access the email ID

Source of Support: None, **Conflict of Interest:** None

DOI: 10.4103/CJP.CJP_1_19

Abstract

One of the principal signaling pathway outcomes from brain-derived neurotrophic factor (BDNF) is the activation of antiapoptotic pathways. In addition to the role of extracellular signal-regulated kinase 1/2 and phosphatidylinositol-3 kinase, BDNF activates protein kinase CK2 to mediate its neuroprotective effect. The inhibition of CK2 activity has been shown to induce apoptosis. Although serum response element (SRE)-mediated transcription has been reported to be activated by BDNF and that the phosphorylation of serum response factor (SRF) by CK2 has been shown to enhance its DNA binding activity, the biological relevance of these interactions remains largely unclear. In the present study, we found that SRE-mediated transcription, CK2 activity, and SRF phosphorylation increased in PC12 cells under BDNF

treatment. The transfection of CK2α siRNA blocked the enhancing effect of BDNF on SRE-mediated transcription, SRF phosphorylation, and *Mcl-1* gene expression. Moreover, the blockade of CK2 diminished the antiapoptotic effects of BDNF on SRE-mediated transcription, *Mcl-1* gene expression, and cell viability under rotenone-induced cytotoxicity. Our data may assist in the development of therapeutic strategies for inhibiting apoptosis during neurodegeneration.

Keywords: Antiapoptosis, brain-derived neurotrophic factor, Mcl-1, protein kinase CK2, serum response element-mediated transcription

How to cite this article:
Yang SP, Lo CY, Tseng HM, Chao CC. Knockdown of protein kinase CK2 blocked gene expression mediated by brain-derived neurotrophic factor-induced serum response element. Chin J Physiol 2019;62:63-9

How to cite this URL:
Yang SP, Lo CY, Tseng HM, Chao CC. Knockdown of protein kinase CK2 blocked gene expression mediated by brain-derived neurotrophic factor-induced serum response element. Chin J Physiol [serial online] 2019 [cited 2020 Feb 19];62:63-9. Available from: http://www.cjphysiology.org/text.asp?2019/62/2/63/257180

Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and is widely distributed in the mammalian brain. Its multiprominent functions include control of neuronal development, modulation of synaptic communication, and neuroprotection. Such a wide spectrum of processes can be explained by the triggering of several signaling pathways.[1],[2] One of the principal signaling pathway outcomes from BDNF is the activation of antiapoptotic pathways. BDNF protects neurons from hypoxia-ischemia injury or phencyclidine-induced cell death through the mediation of extracellular signal-regulated kinase 1/2 (ERK1/2) or phosphatidylinositol-3 kinase (PI3-K) pathways.[3],[4] In addition to the role of ERK1/2 and PI3-K, BDNF activates protein kinase CK2 (formally termed casein kinase II) to mediate its neuroprotective effect.[5]

Protein kinase CK2 is a ubiquitous and multifunctional serine/threonine protein kinase composed of 2 catalytic α or α' subunits and 2 regulatory β subunits.[6] Inhibition of CK2 activity has been shown to induce apoptosis in cancer cells and thus plays a key role in suppressing apoptosis.[7],[8] The global mechanism for inhibiting caspase signaling pathways during apoptosis is thought to be through CK2-mediated phosphorylation.[9] The inhibition of CK2 activity reduces phosphorylation levels of an apoptosis repressor and renders cancer cells susceptible to apoptosis.[10] Moreover, CK2 enhances cell survival through the phosphorylation of the transcription factor NF-κB or serum response factor (SRF) and the subsequent activation of NF-κB- or SRF-mediated pathways.[11],[12]

The transcription factor SRF is activated by serum growth factors and intracellular calcium. In resting cells, SRF mediates the rapid activation of the immediate-early gene *c-fos*.[13] The mitogen-activated protein kinase, Ca^{2+}/calmodulin-dependent kinase, and Rho/actin signaling cascades can trigger SRF-mediated downstream signaling[14] through SRF binding to the serum response element (SRE) in respective promoter regions.[15] In addition to the role of SRF in the regulation of cell growth and differentiation, SRF deficiency leads to decreased antiapoptotic Bcl-2 gene expression during development or MPTP-induced oxidative stress.[16]

Although SRE-mediated transcription is activated by BDNF[17] and the phosphorylation of SRF by CK2 enhances the DNA binding activity of SRF *in vitro*,[18],[19] the biological relevance of these interactions remains unclear. The aim of our study was to determine whether CK2 is involved in the neuroprotective effects of BDNF through the regulation of SRE-mediated transcription.

Materials and Methods

Cell culture

Rat pheochromocytoma (PC12) cells were cultured on the plate precoated with poly-L-lysine and maintained in Dulbecco's modified Eagle's Medium (DMEM) (Gibco) containing 5% fetal bovine serum (FBS) (Gibco) and 10% horse serum (Invitrogen). Cells were incubated at 37°C in a humidified atmosphere with 5% CO_2.

Plasmid construction, siRNA, and transfection

The constructed pGL2-5X SRE-SV40pr by cloning 5 SREs containing ETS-binding sites in front of the SV40 late promoter, and the following firefly luciferase gene of pGL2-Promoter plasmid (Promega) was provided by Dr. Eminy HY Lee.[20] Two sets of CK2α siRNA were used in our previous study.[5] Silencer Negative Control #1 siRNA was used as a control (Ambion). The plasmid and siRNA were transfected to PC12 cells using the Lipofectamine 2000 Transfection Reagent (Invitrogen).

Kinase activity assay

The CK2 enzyme activity assay was performed using the CycLexA CK2 Assay/Inhibitor Screening Kit (MBL International Corporation) according to the manufacturer's instructions. The principle of the experiment was to add a cell extract protein containing CK2 to react with the receptor proteins p53 and ATP and then to use peroxidase-coupled antiphospho-p53 serine46 monoclonal antibody as a reporter molecule, adding cold light reagent to detect cold light signal intensity using the Victor X4 Multilabel Plate Reader (Perkin Elmer).

Promoter-luciferase assay

PC12 cells seeded at a density of 5.4×10^5 cells per well in 12-well clusters were cotransfected with 0.5 μg of pGL2-5X SRE-SV40pr plasmid and 50 ng of internal control Renilla luciferase-encoding plasmid phRG-TK (or cotransfected with siRNA). After 36 h, the medium was replaced with DMEM containing 0.5% FBS. Cells were incubated for 12 h and then subjected to a normal medium (or one containing BDNF) for 6 h for a luciferase activity assay using the FB12 Luminometer (Berthold) with the Dual-Glo Luciferase Assay System (Promega). The ratio of firefly luciferase activity to Renilla luciferase activity was calculated and normalized to the vector control.

Real-time quantitative polymerase chain reaction

Total RNA was isolated from cells as per our previous study.[5] Real-time quantitative polymerase chain reaction (qPCR) analysis was performed using the Applied Biosystems 7300 real-time PCR system with the SYBR Green method according to the instruction manual (Life Technologies). The forward and reverse primer sequences for *Mcl-1* mRNA were 5'-CTTATTTCTTTTGGTGCCTTTGTG-3' and 5'-TCGATGCAGCTTTCTTGGTTT-3', respectively. The endogenous hypoxanthine phosphoribosyl transferase (*HPRT*) gene was used as an internal control. The forward and reverse primer sequences used were 5'-GCCGACCGGTTCTGTCAT-3' and 5'-TCATAACCTGGTTCATCATCACTAATC-3', respectively. The amount of *Mcl-1* and *HPRT* mRNA from each sample was measured simultaneously in separate reactions.

Western blotting

The cells were lysed in a RIPA buffer (50 mM Tris-HCl, 150 mM NaCl, 2 mM EDTA, and 1% IGEPAL CA-630, pH 7.4) with Protease Inhibitor Cocktail Set I (Calbiochem) and the protein Phosphatase Inhibitor Cocktail Set IV (Calbiochem). Equal amounts of lysate samples (20 μg of protein) were subjected to 10% SDS-PAGE and transferred to PVDF membranes (Millipore). The PVDF membranes were blocked with 2% BSA in 0.05% Tween 20 Tris-buffered saline buffer before incubation with one of the following primary antibodies: Anti-pS103SRF (1:1000; Cell Signaling), anti-SRF (1:1000; Millipore), anti-CK2α (1:4000; Abcam), or anti-β-actin (1:10,000; Millipore). A horseradish peroxidase (HRP)-conjugated secondary antibody (Perkin Elmer) was used for all Western blots. The protein bands were visualized using a chemiluminescent HRP substrate and the X-Lite Imaging System (Avegene, Taipei, Taiwan). The density of each band was quantified using ImageJ (NIH).

3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay

Cells were incubated with 3-(4,5-dimethythiazol- 2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reagent (Sigma-Aldrich) at 37°C for 4 h. The amount of MTT formazan product was quantified by measuring its absorbance at 570 and 630 nm using the Victor X4 Multilabel Plate Reader (Perkin Elmer).

Statistical analyses

The data in the present study were evaluated using either Student's *t* test or a one-way ANOVA, followed by a *post hoc* Newman–Keuls multiple comparison test, the results of which are expressed as q values.

Results

Brain-derived neurotrophic factor enhances serum response element-mediated transcription, CK2 activity, and serum response factor phosphorylation

We first examined the effect of BDNF on SRE-mediated gene expression and CK2α enzyme activity. The luciferase assay results revealed that BDNF significantly increased SRE-mediated gene expression [$t_{1,16} = 9.8$, $P < 0.001$; [Figure 1]a. Although the total CK2α protein level did not increase [$t_{1,10} = 0.59$, $P > 0.05$; [Figure 1]b, the BDNF treatment increased CK2 enzyme activity [$t_{1,16} = 20.4$, $P < 0.001$; [Figure 1]c. Because CK2 was shown to phosphorylate SRF at Ser103 and upregulate its transcriptional activity, we also examined the effect of BDNF on SRF phosphorylation at this residue. The BDNF treatment also increased SRF phosphorylation at Ser103 (identical to Ser99 of human SRF) [$t_{1,16} = 6.0$, $P < 0.001$; [Figure 1]d.

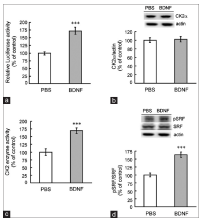


Figure 1: Brain-derived neurotrophic factor increased serum response element-mediated reporter expression, CK2 enzyme activity, and serum response factor phosphorylation. PC12 cells ($1.5 \times 10^5/cm^2$) were transfected with pGL2-5x serum response element-SV40pr plasmid (0.5 μg) for 48 h, followed by 10 ng/mL of brain-derived neurotrophic factor treatment for 6 h. Cells were harvested for (a) a luciferase activity assay by using the Dual-Glo Luciferase Assay System or cells were lysed for a Western blot analysis of (b) CK2, (d) serum response factor phosphorylation at Ser99, and (c) a CK2 enzyme activity assay by using the CycLex CK2 Kinase Assay/Inhibitor Screening Kit ($n = 9$ in each group from three independent batches of cultures). Data are expressed as mean ± standard deviation. Statistical significance was evaluated using Student's *t*-test. ***$P < 0.001$

Click here to view

CK2 regulated serum response element-mediated transcription, serum response factor phosphorylation, and Mcl-1 gene expression

To demonstrate that SRE-mediated gene expression can be regulated by CK2, CK2α siRNA was used to knockdown CK2α protein expression. The results revealed that CK2α siRNA transfection reduced CK2α protein levels [$t_{1,16} = 14.3$, $P < 0.001$; [Figure 2]a. Cotransfection of pGL2-5X SRE-SV40pr plasmid with CK2α siRNA reduced luciferase activity

compared with pGL2-5X SRE-SV40pr plasmid transfection alone [$t_{1,16} = 11.7$, $P < 0.001$; [Figure 2]b, and SRF phosphorylation at Ser99 also decreased in the CK2α siRNA treatment group [$t_{1,16} = 3.67$, $P < 0.01$; [Figure 2]c. Because the SRE element was identified in the promoter region of the antiapoptotic *Mcl-1* gene, the expression of the *Mcl-1* gene was examined using qPCR. The results demonstrated that the *Mcl-1* mRNA level was lower in the cells transfected with CK2α siRNA compared with the control cells [$t_{1,16} = 12.1$, $P < 0.001$; [Figure 2]d.

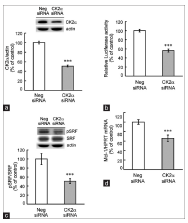


Figure 2: Knockdown of CK2α decreased serum response element-mediated reporter expression, serum response factor phosphorylation, and *Mcl-1* mRNA expression. PC12 cells ($2 \times 10^5/cm^2$) were co-transfected with pGL2-5x serum response elemen-SV40pr plasmid (0.5 μg) and CK2α siRNA (16 pmole) for 48 h and were lysed for a Western blot analysis of (a) CK2, (c) serum response factor phosphorylation at Ser99, and (d) *Mcl-1* mRNA using real-time quantitative polymerase chain reaction or cells were harvested for (b) a luciferase activity assay by using the Dual-Glo Luciferase Assay System or cells (n = 7–11 in each group from three independent batches of cultures). Data are expressed as mean ± standard deviation. Statistical significance was evaluated using Student's t test. ***$P < 0.001$

Click here to view

CK2-mediated the effects of brain-derived neurotrophic factor on serum response element-mediated transcription, serum response factor phosphorylation, and Mcl-1 gene expression

We then examined whether CK2 mediates the effect of BDNF on SRE-mediated gene expression. The results revealed that BDNF consistently increased luciferase activity [$F_{3,38} = 264.3$, $P < 0.001$; q = 20.0, $P < 0.001$; [Figure 3]a and that CK2α siRNA decreased luciferase activity (q = 16.9, $P < 0.001$). However, CK2α siRNA further antagonized the effect of BDNF on luciferase activity (q = 32.5, $P < 0.001$, comparing the BDNF + CK2α siRNA group and BDNF group). Similar results were obtained with SRF phosphorylation; BDNF increased the level of SRF phosphorylation ($F_{3,38}$ = 61.7, q = 10.6, $P < 0.001$). CK2α siRNA alone decreased this level (q = 7.57, $P < 0.001$), but it also blocked the effect of BDNF on SRF phosphorylation [q = 10.9, $P < 0.001$; comparing the BDNF + CK2α siRNA group and BDNF group; [Figure 3]b. In analyzing the *Mcl-1* mRNA level, we revealed that BDNF consistently increased *Mcl-1* mRNA expression [$F_{3,33} = 80.2$, $P < 0.001$; q = 16.0, $P < 0.001$; [Figure 3]c. Moreover, CK2α siRNA alone reduced the *Mcl-1* mRNA level (q = 5.55, $P < 0.001$), but it antagonized the effect of BDNF on *Mcl-1* mRNA expression (q = 11.9, $P <$ 0.001; comparing the BDNF + CK2α siRNA group and BDNF group).

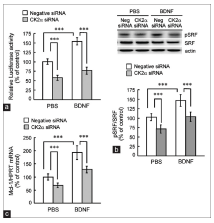


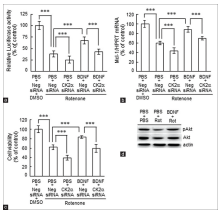
Figure 3: Blockade of CK2α antagonized the effects of brain-derived neurotrophic factor on serum response element-mediated reporter expression, serum response factor phosphorylation, and *Mcl-1* mRNA expression. PC12 cells ($2 \times 10^5/cm^2$) were cotransfected with pGL2-5x serum response element-SV40pr plasmid (0.5 μg) and CK2α siRNA (16 pmole) for 48 h, followed by 10 ng/mL of brain-derived neurotrophic factor treatment for 6 h. The cells were harvested for (a) a luciferase activity assay by using the Dual-Glo Luciferase Assay System or cell lysates were prepared for a Western blot analysis of (b) serum response factor phosphorylation at Ser99 and (c) *Mcl-1* mRNA by using real-time quantitative polymerase chain reaction (n = 8-12 in each group from three independent batches of cultures). Data are expressed as mean ± standard deviation. Statistical significance was evaluated using a one-way ANOVA, followed by the Newman–Kuel method. ***$P < 0.001$

Click here to view

CK2-mediated signaling of brain-derived neurotrophic factor protected cell survival under rotenone-induced cytotoxicity

To determine whether this CK2-mediated signaling contributes to the protective effects of BDNF under stressful stimuli, we examined the signaling pathway under rotenone treatment, because this neurotoxin is widely applied in experimental models of Parkinson disease.[21] CK2α siRNA was transfected into PC12 cells. Transfection occurred for 48 h and then we added BDNF to the medium for 6 h. The cells were then treated with rotenone and incubated for 24 h. The results from the luciferase activity assay showed that rotenone treatment significantly reduced SRE-mediated transcription compared with the control group [$F_{4,50} = 192.3$, $P < 0.001$; q = 28.9, $P < 0.001$; [Figure 4]a and CK2α siRNA aggravated this reduction (q = 6.1, $P < 0.001$ compared with the rotenone group). Prior BDNF treatment prevented rotenone-induced reduction (q = 13.6, $P < 0.001$ compared with the rotenone group), but CK2α siRNA blocked the reversal effect of BDNF (q = 11.6, $P < 0.001$; compared with the BDNF group). Moreover, a qPCR analysis revealed that the *Mcl-1* mRNA level decreased under rotenone treatment compared with that in the control group [$F_{4,30} = 134.6$, $P < 0.001$; q = 19.9, $P <$ 0.001; [Figure 4]b and CK2α siRNA exacerbated this reduction (q = 9.4, $P < 0.001$ compared with the rotenone group). However, rotenone-induced reduction was prevented by prior BDNF treatment (q = 14.4, $P < 0.001$ compared with the rotenone group). However, CK2α siRNA blocked this preventative effect of BDNF (q = 9.8, $P < 0.001$ compared with the BDNF group). Furthermore, rotenone treatment reduced cell viability [$F_{4,49} = 174.1$, $P < 0.001$; q = 21.3, $P < 0.001$; compared with the control group; [Figure 4]c and CK2α siRNA encouraged this reduction (q = 13.1, $P < 0.001$ compared with the rotenone group). However, prior BDNF treatment promoted cell viability compared with rotenone treatment alone (q = 12.5, $P < 0.001$). The blockade of CK2α by siRNA diminished the protective effect of BDNF on cell survival (q = 13.8, $P < 0.001$). In order to verify the protective signaling by BDNF is activated under the rotenone-induced stress, we examined the Akt phosphorylation at Ser473 residue. The rotenone treatment decreased Akt phosphorylation but prior BDNF treatment prevented this reduction [Figure 4]d.

Figure 4: Blockade of CK2α suppressed the protective effects of brain-derived neurotrophic factor on serum response element-mediated reporter expression, *Mcl-1* mRNA expression, and cell viability. PC12 cells ($2 \times 10^5/cm^2$) were transfected with 16 pmole of CK2α siRNA for 48 h, followed by 10 ng/mL of brain-derived neurotrophic factor treatment for 6 h. The cells then received 500 nM of rotenone treatment for 24 h.



The cells were harvested for (a) a luciferase activity assay by using the Dual-Glo Luciferase Assay System, (b) *Mcl-1* mRNA by using real-time quantitative polymerase chain reaction, (c) cell viability determination by using an 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay ($n = 9$ in each group from three independent batches of cultures). (d) The protein profile of Akt phosphorylation at Ser473 by the Western blot analysis. Data are expressed as mean ± standard deviation. Statistical significance was evaluated using a one-way ANOVA followed by the Newman–Kuel method. ***$P < 0.001$

Click here to view

Discussion

The present study demonstrated that the activation of SRE-mediated gene transcription by BDNF can be blocked through knockdown of protein kinase CK2. This result is consistent with the previous study showed that SRE-mediated gene expression as a downstream for the neuroprotective mechanism of BDNF[17] and CK2 signaling is an alternative pathway, enabling BDNF to produce its effect independent of ERK1/2 and PI3-K activation.[5] Severe impairment of SRE-driven promoter activity was observed in apoptotic cells through the activation of death receptors.[22] A set of genes that have SRF sites in their promoters are also repressed in breast epithelial cells under Myc-induced apoptosis.[23] In the present study, SRE-driven luciferase activity significantly decreased under the rotenone treatment, parallel with cell viability, but was restored by the BDNF treatment. These results are consistent with a study that reported that the knockdown of SRF augmented rotenone-induced toxicity[24] and a study that reported that BDNF secreted from astrocytes significantly attenuated rotenone-induced DA neuron injury *in vitro*.[25]

The PI3-K/Akt and ERK1/2 pathways are thought to be predominant downstream cascades of BDNF that control numerous prosurvival mechanisms, such as CREB-Bcl-2 and NFκB-Bcl-xL expressions.[1] In our previous study, we showed that BDNF, as an alternative pathway, could enhance Bcl-xL expression through CK2-NFκB signaling[5] and CK2 also increased apoptotic *Mcl-1* gene expression in an SRF-dependent manner.[12] Inhibition CK2 is reported to cause elevated levels of ROS and mitochondrial dysfunction.[26] Furthermore, aripiprazole, an atypical antipsychotic drug, has been reported to restore reduced BDNF and phospho-CK2α expression caused by $A\beta_{1-42}$.[27] Our current results also showed that BDNF-induced SRF phosphorylation was reduced by the knockdown of CK2. Taken together, these results indicate that CK2-mediated signaling contributes to the antiapoptotic effects of BDNF. BDNF is known to possess other neuroprotective effects including anti-oxidation and suppression of autophagy.[28] Further, BDNF enhances sestrin2 expression to confer neuronal resistance against oxidative stress through activation of PKG/NF-κB signaling pathway.[29] Whether CK2 signaling cascades cross-talk with other BDNF-activated signaling pathways to regulate neuroprotective effects warrants further investigation.

The promoter of *Mcl-1* contains a functional SRE.[30] The reduction in *Mcl-1* gene expression and induction of apoptosis were found in smooth muscle cells by the silence of SRF.[31] Furthermore, overexpression of SRF cofactor MRTF-A was found to trigger the transcription activity of the *Mcl-1* reporter gene in cortical neurons.[32] The blockade of SRF reversed the subtle dosage of a glutamate-induced increase in Mcl-1 protein level.[12] Thus, the above-mentioned studies have suggested that the regulation of *Mcl-1* gene expression occurs in an SRF-dependent manner. In addition to SRF, the phosphorylation of STAT1 by CK2 or SGK has been shown to promote *Mcl-1* gene expression.[33],[34] *Mcl-1* gene expression was also downregulated under CREB suppression.[35],[36] How SRF synergizes with other transcription factors to upregulate *Mcl-1* gene expression warrants further investigation. In addition, an increase in *Mcl-1* mRNA and protein levels in AICAR-preconditioned cortical neurons was reported.[37] Such antiapoptotic functions in diseased cells suggest that Mcl-1 is a potential target for clinical therapy.

Conclusion

In summary, the blockade of CK2 inhibited BDNF-induced SRE-mediated transcription, such as antiapoptotic *Mcl-1* gene expression. Our findings suggest an alternative cellular mechanism for the attenuation of cell death, which may assist in the development of therapeutic strategies for inhibiting apoptosis.

Acknowledgment

The authors would like to thank Dr. Eminy HY Lee from the Institute of Biomedical Sciences, Academia Sinica in Taiwan for providing plasmids. This manuscript was edited by Wallace Academic Editing.

Financial support and sponsorship

This work was supported by a grant from the Ministry of Science and Technology, Taiwan, Republic of China (NSC 96-2320-B-320-012-MY2).

Conflicts of interest

There are no conflicts of interest.

References

1. Zhao H, Alam A, San CY, Eguchi S, Chen Q, Lian Q, *et al.* Molecular mechanisms of brain-derived neurotrophic factor in neuro-protection: Recent developments. Brain Res 2017;1665:1-21.

2. Kowiański P, Lietzau G, Czuba E, Waśkow M, Steliga A, Moryś J. BDNF: A Key factor with multipotent impact on brain signaling and synaptic plasticity. Cell Mol Neurobiol 2018;38:579-93.

3. Han BH, Holtzman DM. BDNF protects the neonatal brain from hypoxic-ischemic injury *in vivo* via the ERK pathway. J Neurosci 2000;20:5775-81.

4. Xia Y, Wang CZ, Liu J, Anastasio NC, Johnson KM. Brain-derived neurotrophic factor prevents phencyclidine-induced apoptosis in developing brain by parallel activation of both the ERK and PI-3K/Akt pathways. Neuropharmacology 2010;58:330-6.

5. Chao CC, Ma YL, Lee EH. Brain-derived neurotrophic factor enhances Bcl-xL expression through protein kinase casein kinase 2-activated and nuclear factor kappa B-mediated pathway in rat hippocampus. Brain Pathol 2011;21:150-62.

6. Litchfield DW. Protein kinase CK2: Structure, regulation and role in cellular decisions of life and death. Biochem J 2003;369:1-5.

7. Ahmad KA, Wang G, Unger G, Slaton J, Ahmed K. Protein kinase CK2 – A key suppressor of apoptosis. Adv Enzyme Regul 2008;48:179-87.

8. Hanif IM, Hanif IM, Shazib MA, Ahmad KA, Pervaiz S. Casein kinase II: An attractive target for anti-cancer drug design. Int J Biochem Cell Biol 2010;42:1602-5.

9. Duncan JS, Turowec JP, Duncan KE, Vilk G, Wu C, Lüscher B, *et al.* A peptide-based target screen implicates the protein kinase CK2 in the global regulation of caspase signaling. Sci Signal 2011;4:ra30.

10. Wang J, Feng C, He Y, Ding W, Sheng J, Arshad M, *et al.* Phosphorylation of apoptosis repressor with caspase recruitment domain by protein kinase CK2 contributes to chemotherapy resistance by inhibiting doxorubicin induced apoptosis. Oncotarget 2015;6:27700-13.

11. Manna SK, Manna P, Sarkar A. Inhibition of relA phosphorylation sensitizes apoptosis in constitutive NF-kappaB-expressing and chemoresistant cells. Cell Death Differ 2007;14:158-70.

12. Chang CM, Chao CC. Protein kinase CK2 enhances Mcl-1 gene expression through the serum response factor-mediated pathway in the rat hippocampus. J Neurosci Res 2013;91:808-17.

13. Herdegen T, Leah JD. Inducible and constitutive transcription factors in the mammalian nervous system: Control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins. Brain Res Brain Res Rev 1998;28:370-490.

14. Knöll B, Nordheim A. Functional versatility of transcription factors in the nervous system: The SRF paradigm. Trends Neurosci 2009;32:432-42.

15. Chai J, Tarnawski AS. Serum response factor: Discovery, biochemistry, biological roles and implications for tissue injury healing. J Physiol Pharmacol 2002;53:147-57.

16. Rieker C, Schober A, Bilbao A, Schütz G, Parkitna JR. Ablation of serum response factor in dopaminergic neurons exacerbates susceptibility towards MPTP-induced oxidative stress. Eur J Neurosci 2012;35:735-41.

17. Chang SH, Poser S, Xia Z. A novel role for serum response factor in neuronal survival. J Neurosci 2004;24:2277-85.

18. Manak JR, Prywes R. Mutation of serum response factor phosphorylation sites and the mechanism by which its DNA-binding activity is increased by casein kinase II. Mol Cell Biol 1991;11:3652-9.

19. Marais RM, Hsuan JJ, McGuigan C, Wynne J, Treisman R. Casein kinase II phosphorylation increases the rate of serum response factor-binding site exchange. EMBO J 1992;11:97-105.

20. Tyan SW, Tsai MC, Lin CL, Ma YL, Lee EHY. Serum- and glucocorticoid-inducible kinase 1 enhances *zif268* expression through the mediation of SRF and CREB1 associated with spatial memory formation. J Neurochem 2008;105:820-32.

21. Drechsel DA, Patel M. Role of reactive oxygen species in the neurotoxicity of environmental agents implicated in Parkinson's disease. Free Radic Biol Med 2008;44:1873-86.

22. Bertolotto C, Ricci JE, Luciano F, Mari B, Chambard JC, Auberger P. Cleavage of the serum response factor during death receptor-induced apoptosis results in an inhibition of the c-FOS promoter transcriptional activity. J Biol Chem 2000;275:12941-7.

23. Wiese KE, Haikala HM, von Eyss B, Wolf E, Esnault C, Rosenwald A, *et al.* Repression of SRF target genes is critical for Myc-dependent apoptosis of epithelial cells. EMBO J 2015;34:1554-71.

24. Cheng XY, Li SY, Mao CJ, Wang MX, Chen J, Wang F, *et al.* Serum response factor promotes dopaminergic neuron survival via activation of beclin 1-dependent autophagy. Neuroscience 2018;371:288-95.

25. Yang D, Peng C, Li X, Fan X, Li L, Ming M, *et al.* Pitx3-transfected astrocytes secrete brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor and protect dopamine neurons in mesencephalon cultures. J

Neurosci Res 2008;86:3393-400.

26. Schaefer S, Guerra B. Protein kinase CK2 regulates redox homeostasis through NF-κB and Bcl-xL in cardiomyoblasts. Mol Cell Biochem 2017;436:137-50.

27. Park SY, Shin HK, Lee WS, Bae SS, Kim K, Hong KW, *et al.* Neuroprotection by aripiprazole against β-amyloid-induced toxicity by P-CK2α activation via inhibition of GSK-3β. Oncotarget 2017;8:110380-91.

28. Chen SD, Wu CL, Hwang WC, Yang DI. More insight into BDNF against neurodegeneration: Anti-apoptosis, anti-oxidation, and suppression of autophagy. Int J Mol Sci 2017;18. pii: E545.

29. Wu CL, Chen SD, Yin JH, Hwang CS, Yang DI. Nuclear factor-kappaB-dependent sestrin2 induction mediates the antioxidant effects of BDNF against mitochondrial inhibition in rat cortical neurons. Mol Neurobiol 2016;53:4126-42.

30. Vickers ER, Kasza A, Kurnaz IA, Seifert A, Zeef LA, O'donnell A, *et al.* Ternary complex factor-serum response factor complex-regulated gene activity is required for cellular proliferation and inhibition of apoptotic cell death. Mol Cell Biol 2004;24:10340-51.

31. Rodenberg JM, Hoggatt AM, Chen M, Touw K, Jones R, Herring BP. Regulation of serum response factor activity and smooth muscle cell apoptosis by chromodomain helicase DNA-binding protein 8. Am J Physiol Cell Physiol 2010;299:C1058-67.

32. Cao XL, Hu XM, Hu JQ, Zheng WX. Myocardin-related transcription factor-A promoting neuronal survival against apoptosis induced by hypoxia/ischemia. Brain Res 2011;1385:263-74.

33. Timofeeva OA, Plisov S, Evseev AA, Peng S, Jose-Kampfner M, Lovvorn HN, *et al.* Serine-phosphorylated STAT1 is a prosurvival factor in Wilms' tumor pathogenesis. Oncogene 2006;25:7555-64.

34. Hsu WL, Chiu TH, Tai DJ, Ma YL, Lee EH. A novel defense mechanism that is activated on amyloid-beta insult to mediate cell survival: Role of SGK1-STAT1/STAT2 signaling. Cell Death Differ 2009;16:1515-29.

35. Shabestari RM, Safa M, Alikarami F, Banan M, Kazemi A. CREB knockdown inhibits growth and induces apoptosis in human pre-B acute lymphoblastic leukemia cells through inhibition of prosurvival signals. Biomed Pharmacother 2017;87:274-9.

36. Shichiri H, Yamamoto K, Tokura M, Ishida T, Uda A, Bito T, *et al.* Prostaglandin E1 reduces the keratinocyte toxicity of sorafenib by maintaining signal transducer and activator of transcription 3 (STAT3) activity and enhancing the cAMP response element binding protein (CREB) activity. Biochem Biophys Res Commun 2017;485:227-33.

37. Anilkumar U, Weisová P, Düssmann H, Concannon CG, König HG, Prehn JH. AMP-activated protein kinase (AMPK)-induced preconditioning in primary cortical neurons involves activation of MCL-1. J Neurochem 2013;124:721-34.

Figures

[Figure 1], [Figure 2], [Figure 3], [Figure 4]

ISSN: Print -0304-4920, Online - 2666-0059