[11] 曹延萍, 郝咏梅, 刘青娟, 等. 内质网应激及其特有凋亡途径 Caspase-12 与糖尿病大鼠肾组织固有细胞凋亡之间的关系. 中国应用生理学杂志, 2011, 27(2):236 - 240.

[12] Hu E, Mueller E, Oliviero S, et al. Targeted disruption of the c-fos gene demonstrates c-fos-dependent and -independent pathways for gene expression stimulated by growth factors or oncogenes [J]. EMBO J, 1994, 13(13): 3094 - 3103.

[13] Liu CM, Zheng GH, Ming QL, et al. Protective effect of quercetin on lead-induced oxidative stress and endoplasmic reticulum stress in rat liver via the IRE1 /JNK and PI3K/Akt pathway [J]. Free Radic Res, 2013, 47: 192 - 201.

[14] Gorin Y, Ricono JM, Wagner B, et al. Angiotensin II-induced ERKl/ERK2 activation and protein synthesis are redox-dependent in glomerular mesangial cells [J]. Biochem J, 2004, 381(Pt 11): 231 - 239.

[15] Iturralde M, Gamen S, Pardo J, et al. Saturated free fatty acid release and intracellular ceramide generation during apoptosis induction are closely related processes [J]. Biochim Biophys Acta, 2003, 16(34): 40 - 51.

[16] Wang WZ, Pang L, Palade P, et al. Angiotensin II causes endothelial dependent increase in expression of Ca protein in cultured arteries [J]. Eur Pharmacol, 2008, 599: 117 - 120.

[收稿日期] 2014-11-19

·国际前沿·

【编者按】本文为丹尼尔整理 2014 年博士期间工作,发表在《neurobiology of disease》上的研究论文。他结合 2014 年本刊第 6 期向读者解读的:神经功能原理模型对研究者的重要指导作用。从自身实际研究的角度,谈了自己选题、设计、实施……的体会。本文有助于读者和研究人员今后的研究实践。

Topics of interest – 'Targeting Regulators of G-protein signalling (RGS) proteins in movement disorders'

Following on from the last article on the descriptions of the basal ganglia model in movement disorders (3rd edition); this related communication refers to our recently published research (Ko et al., 2014) on the pathophysiological roles of RGS proteins in Parkinson's disease (PD) and L-DOPA-induced dyskinesia (LID).

Although the cause of LID remains unknown, evidence has suggested that repeated, pulsatile stimulation of the dopamine receptors in the basal ganglia contributes to the development of LID. This process is commonly referred to as 'priming' and is the abnormal long-term stimulation of dopamine receptor subtypes, which belong to the well-known class of proteins called G-protein coupled receptors (GPCRs). Ultimately, priming causes abrupt functional changes in second messenger signalling mechanisms (Aubert et al., 2005) that lead to the development and expression of dyskinesia.

In our published paper (Ko et al., 2014), we focused our attention on RGS proteins which are known to modulate GPCRs (Hepler, 1999). Specifically, we investigated the role of RGS protein subtype 4 and its pathophysiological role in the expression of PD and LID motor symptoms. Our experiments utilised the well-established 6-hydroxydopamine (6-OHDA)-lesioned rat model (Cenci et al., 1998) and progressed from a series of in vivo to in vitro explorations, in an attempt to fully characterise the functional changes of RGS4 in PD and LID.

The main findings from our research demonstrated that RGS4 proteins were involved in the expression of LID. This was seen following correlation analyses ($r = 0.93$, $P < 0.06$) of RGS4 mRNA with abnormal involuntary movements (AIMs) in L-DOPA-treated 6-OHDA-lesioned rats. Thereafter, we innovatively suppressed the expression of RGS4 mRNA using antisense oligonucleotides, which were chronically delivered into the brain through osmotic mini-pumps. We found that dampening the expression of RGS4 mRNA was able to reduce the induction of AIMs and the subsequent development of marked molecular changes associated with LID, such as dopamine receptor super-sensitisation. Our key findings indicated that such second messenger signalling proteins may provide for novel therapeutic targets for the treatment of movement disorders and/ or other neurological disorders.

References

Aubert I, Guigoni C, Håkansson K, Li Q, Dovero S, Barthe N, Bioulac BH, Gross CE, Fisone G, Bloch B, Bezard E. Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia. Ann Neurol. 2005;57(1):17 - 26.

Cenci MA, Lee CS, Björklund A. L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA. Eur J Neurosci. 1998;10(8):2694 - 2706.

Hepler JR. Emerging roles for RGS proteins in cell signalling. Trends Pharmacol Sci. 1999;20(9):376 - 382.

Ko WK, Martin-Negrier ML, Bezard E, Crossman AR, Ravenscroft P. RGS4 is involved in the generation of abnormal involuntary movements in the unilateral 6-OHDA-lesioned rat model of Parkinson's disease. Neurobiol Dis. 2014;70: 138 - 148.

栏目主持:李秦