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NEWS & VIEWS

Transcriptional pharmacology of neurodegenerative disorders: novel venue towards neuroprotection against excitotoxicity?

Transcription factors NF-κB/Rel represent the point of convergence of several signalling pathways relevant to neurodegeneration. The finding that salicylates elicit neuroprotection via blockade of NF-κB provides new opportunities for pharmacological intervention.

The term neurodegenerative as applied to diseases of the nervous system is used to designate a group of disorders in which there is gradual, generally symmetric, relentlessly progressive wasting away of neurons for reasons still unknown. A striking feature of a number of disorders of this class is the almost selective involvement of anatomically and physiologically related subgroups of neurons. The abnormal loss of neurons that may occur during development or as a result of an injury represents the functional substrate of many symptoms easily detectable in a number of neurological and psychiatric disorders. The understanding of the mechanisms that account for specific neuronal dysfunction and death in these diseases represents a major challenge for both clinical and basic neuroscientists.

In the last years dysfunction of the ionotropic glutamate-activated neurotransmitter receptors, which are the principal providers of fast neurotransmission in mammalian brain, has been extensively implicated since excessive or persistent activation of these receptors results in neuronal death by excitotoxicity.[1] Brain damage through excitotoxicity has been closely associated with acute conditions like stroke, trauma, ischaemia, hypoglycemia, but also with epilepsy and ALS. A contribution of excitotoxicity to chronic and progressive neuropathologies like Alzheimer's and Parkinson's diseases has also been suggested.[2]

Interference with glutamate receptor function has been extensively explored as a means to develop compounds able to attenuate or prevent excitotoxicity. More recently, the search for novel targets for pharmacological manipulation of excitotoxicity has been directed towards the intracellular events triggered by neurotoxic concentrations of glutamate. This approach has allowed us to reach down to the nuclear participants of the glutamate-evoked cell death program including transcription factors and their targeted genes.[3] Among the transcription factors that are activated by glutamate in neuronal cells, there are proteins belonging to the NF-κB/Rel family.[4] Recent work suggests a pivotal role of these regulatory proteins along the glutamate-evoked cascade of events leading to cell death since blockade of their activation can result in effective neuroprotection.[5]

Until recently, the properties of NF-κB/Rel proteins have been most extensively exploited in cells of the immune system or, more in general, in periphery, where these regulators are implicated in the transcriptional control of genes involved in inflammatory, immune, and acute phase responses.[4] Some recent reports have suggested that NF-κB/Rel proteins are likely to participate in normal and pathological brain function.[6–8] Despite these important contributions, very little is known on the CNS genes whose expression is under NF-κB control. We recently found that two major pathogenic pathways which are likely to contribute to the neuropathology associated with Alzheimer's disease, namely the inflammatory cytokine IL-1β and glutamate, can contribute to NF-κB induction.[9–10] We also tested whether anti-inflammatory drugs, and aspirin in particular, may prevent glutamate-induced NF-κB activation in neuronal cells. Why aspirin? There are several reasons that made these drugs extremely interesting from our point of view. First, clinical and experimental evidence has suggested that inflammation may be a common component of several neurodegenerative conditions, in particular of AD (reviewed by McGeer[11]). Various inflammatory cells (activated microglia) and mediators (cytokines, complement factors, acute phase reactants) are commonly found closely associated to plaques or degenerating neurons. Second, several retrospective epidemiological studies showed a lower incidence of Alzheimer's disease in patients who received chronic

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anti-inflammatory therapy for treatment of rheumatoid arthritis.[11] In a small clinical trial, indomethacin has demonstrated some efficacy in slowing down progression in people affected by AD.[12] Finally, Kopp and Gosh[13] showed that salicylates are endowed with the ability to block NF-κB activation. This mechanism has been purported to be highly contributory to the pharmacological properties of these drugs since the key role of NF-κB proteins is controlling immune and inflammatory function.

Under these exciting premises, we tested whether, at concentrations compatible with plasma levels reached during treatment of chronic inflammatory states, aspirin and sodium salicylate may interfere with glutamate-induced activation of NF-κB and cell death. Both drugs turned out to be effectively neuroprotective. Surprisingly, the neuroprotective effect did not appear to correlate with the anti-inflammatory properties of this compound since: (i) indomethacin was inactive; (ii) in our experimental settings, aspirin was equi- or more potent than its metabolite salicylic acid. The molecular target for aspirin and sodium salicylate to exert neuroprotection appeared to be localized downstream of the glutamate receptor. Along the cascade of events triggered by stimulation of the NMDA-subtype of glutamate receptor, the compounds were in particular able to counteract the glutamate-mediated induction of NF-κB activity. A strict correlation was observed between doses of the drugs able to prevent cell death and to block induction of the nuclear activity. The effect was specific, since under the same conditions glutamate-mediated induction of AP-1, another transcription factor specifically activated by glutamate receptor stimulation, was unaffected. Since these data were obtained *in vitro*, an easy objection to be raised would be: what is the relevance of these transcriptional mechanisms *in vivo* and in pathophysiology? Several observations are suggestive for a role of NF-κB proteins in brain dysfunction *in vivo* and in particular in AD. Yan *et al*[14] and Terai *et al*[15] have demonstrated augmented NF-κB activity in brains of AD patients compared to age-matched controls. More importantly, NF-κB upregulated activity and signs of neuronal sufferance appeared to colocalize in the same neuron subsets.

The role of NF-κB/Rel proteins in neurodegeneration may even be wider than expected. We propose that NF-κB/Rel proteins may indeed represent the point of convergence of several signalling pathways relevant for initiating or accelerating the process of neuronal dysfunction and degeneration in AD and maybe in other neurodegenerative disorders. If NF-κB/Rel proteins represent an integrating point which conveys pathways potentially contributing to the neurodegeneration associated with several neurological diseases, molecules that finely modulate their activity could also prevent and/or retard the progression of the disease. Thus the finding that salicylates can prevent excitotoxicity via blockade of NF-κB activation acquires a broader significance. The implications of the novel and unexpected pharmacological property of salicylates in clinical use and in particular in acute and chronic neurodegenerative disorders has still to be evaluated but it could be of great relevance. These molecules would appear to possess a wider pharmacological spectrum compared to other NSAID. In view of their dual and distinct ability of acting not merely as anti-inflammatory compounds but also directly as antidegenerative molecules, we would predict a potential great benefit from the employment of aspirin-derived drugs in neurodegenerative processes. Furthermore these results may open up interesting perspectives in the development of novel strategies for therapeutic intervention in neurodegenerative states, namely a transcriptional pharmacological approach.

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References

1 Choi DW. Glutamate neurotoxicity and diseases of the nervous system. *Neuron* 1988; **1**: 623–634.
2 Lipton BT, Rosenberg PA. Excitatory aminoacids as a final common pathway for neurological disorders. *New Engl J Med* 1995; **330**: 613–622.
3 Memo M, Pizzi M, Valerio A, Grilli M, Spano PF. Molecular mechanisms of glutamate-induced neurodegeneration. *Int Rev Psych* 1995; **7**: 339–348.
4 Grilli M, Chiu J-S, Lenardo MJ. NF-κB and Rel: participants in a multiform transcriptional regulatory system. *Int Rev Cytol* 1993; **143**: 1–62.
5 Grilli M, Pizzi M, Memo M, Spano PF. Neuroprotection by aspirin and sodium salicylates through blockade of NF-κB activation. *Science* 1996; **274**: 1383–1385.
6 Kaltschmidt C, Kaltschmidt B, Neumann H, Wekerle H, Bauerle PA. Constitutive NF-κB activity in neurons. *Mol Cell Biol* 1994; **14**: 3981–3992.
7 Kaltschmidt C, Kaltschmidt B, Baeuerle PA. Stimulation of ionotropic glutamate receptors activates transcription factor NF-κB in primary neurons. *Proc Natl Acad Sci USA* 1995; **92**: 9618–9622.
8 Guerrini L, Blasi F, Denis-Donini S. Synaptic activation of NF-κB by glutamate in cerebellar granule neurons *in vitro*. *Proc Natl Acad Sci USA* 1995; **92**: 9077–9081.
9 Grilli M, Ribola M, Alberici A, Valerio A, Memo M, Spano PF. Identification and characterization of a NF-κB/Rel binding site in the regulatory region of the Amyloid Precursor Protein gene. *J Biol Chem* 1995; **270**: 26774–26777.
10 Grilli M, Goffi F, Memo M, Spano PF. Interleukin-1β and glutamate activate the NF-κB/Rel binding site from the regulatory region of the Amyloid Precursor Protein gene in primary neuronal cultures. *J Biol Chem* 1996; **271**: 15002–15007.
11 McGeer PL, McGeer EG. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res Rev* 1995; **21**: 195–218.
12 Rogers J, Kirby LC, Hempelman SR, Berry DL, McGeer PL, Kaszniak AW, Zalinski J, Cofield M, Manuskhani L, Willson P, Kogan F. Clinical trial of indomethacin in Alzheimer's disease. *Neurology* 1993; **43**: 1609–1611.

13 Kopp E, Ghosh S. Inhibition of NF-κB activity by sodium salicylate and aspirin. *Science* 1994; **265**: 956–959.
14 Yan SD, Yan SF, Chen X, Fu J, Chen M, Kuppusamy P, Smith MA, Perry G, Godman GC, Nawroth P, Zweier JL, Stern D. Non-enzymatically glycated tau in Alzheimer's disease induces oxidant stress resulting in cytokine gene expression and release of amyloid β-peptide. *Nature Medicine* 1995; **1**: 693–699.
15 Terai K, Matsuo A, McGeer P. Enhancement of immunoreactivity for NF-κB in the hippocampal formation and cerebral cortex of Alzheimer's disease. *Brain Res* 1996; **735**: 159–169.