INDUCTION OF THE WNT ANTAGONIST, DICKKOPF-1, AS A MARKER OF EXCITOTOXIC NEURONAL DEATH

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Dickkopf-1 (Dkk-1) is a secreted glycoprotein that acts as an extracellular inhibitor of the canonical Wnt/β-catenin/TCF/LEF pathway by interacting with the Wnt co-receptors, low-density lipoprotein-related protein receptors, type 5 and -6 (LRP5/6). Inhibition of the canonical Wnt pathway produces a series of intracellular events that may be detrimental to neurons, including a reduced availability of free β-catenin available for the regulation of gene expression, and an increased phosphorylation of the tau protein. Both events are driven by a disinhibition of glycogen synthase kinase-3β (GSK-3β), an enzyme that is negatively regulated by the Wnt pathway. We found that Dkk-1 is induced in cultured cortical neurons challenged with toxic concentrations of N-methyl-D-aspartate. This induction is associated with a reduction of nuclear levels of β-catenin, and consistently precedes neuronal death. Remarkably, both Dkk-1 antisense oligonucleotides and lithium ions (which inhibit GSK-3β) protect cultured neurons against excitotoxic death. We also found a substantial induction of Dkk-1 in vulnerable neurons (e.g. pyramidal cells of the hippocampal CA1 region) of gerbils or rats subjected to transient global brain ischemia. Induction of Dkk-1 again preceded neuronal death and was associated with an increased expression of p53, an established sensor of DNA damage. A likely scenario is that the DNA damage produced by the ischemic insult increases p53 levels, and that p53 acts as transcriptional activator of the Dkk-1 gene, thus amplifying neuronal damage. More recently, we have found that Dkk-1 is also induced (i) in the perifocal region of rats subjected to focal brain ischemia induced by local infusion of endothelin-1 in the territory of the middle cerebral artery; and (ii) in vulnerable cortical and hippocampal neurons of rats developing secondarily generalized limibic motor seizures in response to systemic injection of kainic acid. Interestingly, Dkk-1 is also expressed by hippocampal neurons of patients with temporal lobe epilepsy associated with Ammon's horn sclerosis. Taken collectively, these data strongly suggest that Dkk-1 is a marker of excitotoxic death and contributes to the death cascade in acute and chronic neurodegenerative disorders.