



DOTTORATO INTERNAZIONALE  
IN NEUROFARMACOLOGIA

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# IL PROMETEO



Bollettino di Dottorato

Direttore: Prof. Filippo Drago

## PUBBLICAZIONI DEL DOTTORATO INTERNAZIONALE IN NEUROFARMACOLOGIA (2007 - 2008)

*J Ocul Pharmacol Ther.* 2007 Jun;23(3):232-9.

### **Hemin, an inducer of heme oxygenase-1, lowers intraocular pressure in rabbits.**

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**AIM:** Carbon monoxide (CO) generated from heme may induce vasodilation and exert cyto-protective properties in the eye. This study was undertaken to investigate the effects of hemin, a potent inducer of heme oxygenase-1 (HO-1), on models of ocular hypertension in rabbits.

**METHODS:** Ocular hypertension was induced by injecting alpha-chymotrypsin in both eyes under local anesthesia. Only rabbits with an intraocular pressure (IOP) of 25 mmHg or more were used. The dose-response study of the hemin effect on IOP was made by an intravenous injection of the drug (50, 75, and 100 mg/kg) and subsequent IOP monitoring every 6 h. A separate set of animals was pretreated with the HO-1 inhibitor, zinc protoporphyrin-IX (ZnPP-IX, 0.1 mg/kg) 6 h before the vehicle or a 100-mg/kg hemin injection. Ocular hypertension was also obtained by the subconjunctival injection of betamethasone 21-phosphate disodium (4 mg/mL) in both eyes every week for 4 weeks. Only animals with an IOP of 30 mmHg or more were included in the experimental session. A group of these animals was pretreated with ZnPP-IX (0.1 mg/kg) 6 h before the vehicle or a 100-mg/kg hemin injection, and IOP was assessed every 6 hours.

**RESULTS:** Hemin caused a significant dose-related reduction of IOP in rabbits with alpha-chymotrypsin-induced ocular hypertension. No significant effect was observed in the normotensive eyes of the control animals or on pupil diameter. Pretreatment with the HO-1 inhibitor, ZnPP-IX, abolished the decrease of IOP that was induced by the maximum dose of hemin (100 mg/kg). A similar reduction in IOP was observed in those rabbits with betamethasone-induced ocular hypertension who were treated with 100 mg/kg of hemin. Furthermore, pretreatment with ZnPP-IX prevented the hemin effect on IOP. **CONCLUSIONS:** The induction of HO-1 by hemin leads to a reduction of IOP in the alpha-chymotrypsin and betamethasone models of ocular hypertension. These results suggest an involvement of CO in the regulation of ocular pressure in rabbits.

*Am J Clin Nutr.* 2007 Sep;86(3):775-80.

### **Influence of inulin on plasma isoflavone concentrations in healthy postmenopausal women.**

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**BACKGROUND:** Bacterial intestinal glucosidases exert an important role in isoflavone absorption. Insoluble dietary fibers such as inulin may stimulate the growth of these bacteria in the colon and, hence, stimulate the absorption of these substances in subjects who may need isoflavone supplementation.

**OBJECTIVE:** The objective was to assess the influence of inulin on plasma isoflavone concentrations after intake of soybean isoflavones in healthy postmenopausal women.

**DESIGN:** Twelve healthy postmenopausal women participated in a randomized, double-blind, crossover study. They consumed 40 mg of a conjugated form of soybean isoflavones (6 mg daidzein and 18 mg genistein as free form) with or without 3.66 g inulin twice daily in two 21-d experimental phases. Blood samples were collected 0, 1, 2, 3, 4, 6, 10,



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12, and 24 h after intake of isoflavones with breakfast and dinner at the end of each 21-d experimental phase. Plasma concentrations of isoflavones were assessed by HPLC with an electrochemical detector.

**RESULTS:** Plasma 24-h areas under the curve indicated that the intake of soybean isoflavones with inulin for 21 d was followed by higher plasma concentrations of daidzein and genistein (38% and 91%, respectively) compared with the formulation without inulin. Furthermore, the time for the maximum concentration of daidzein and genistein appeared to be lower after the 21-d intake of soybean isoflavones, with or without inulin. However, the time for the maximum concentration of daidzein and genistein after supplementation with the inulin-containing formulation on day 21 was not significantly different from that after supplementation with the formulation without inulin.

**CONCLUSIONS:** Inulin may increase the apparent plasma concentrations of the soybean isoflavones daidzein and genistein in postmenopausal women. The higher plasma concentrations of the 2 isoflavones suggests that the absorption of each was facilitated by the presence of inulin.

*Eur J Pharmacol.* 2007 Nov 14;573(1-3):139-47. Epub 2007 Jul 4.

### **Behavioral effects of the beta3 adrenoceptor agonist SR58611A: is it the putative prototype of a new class of antidepressant/anxiolytic drugs?**

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A large body of evidence corroborates the notion that deficiencies of serotonergic system are likely involved in the pathogenesis of both depression and anxiety. Activation of beta(3) adrenoceptors has been shown to increase brain tryptophan content suggesting an elevation of brain serotonin (5HT) synthesis. SR58611A is a selective beta(3) adrenergic agent possessing a profile of antidepressant activity in routine rodents' experimental models of depression. The present study was undertaken to evaluate in rodents the antidepressant properties of SR58611A and to assess its putative anxiolytic value in experimental models of depression and anxiety. Compared to the control group, SR58611A (0.1, 1, 5 or 10 mg/kg) caused a dose-dependent reduction in immobility of Wistar male rats in the forced swim test. The maximum dose appeared to be equivalent to an effective dose of clomipramine (50 mg/kg). In addition, acute injection of SR58611A induced in rats a dose-dependent decrease in grooming response to a novel environment (novelty-induced grooming test). For any dose, the effect was lower than that of diazepam (1 mg/kg). Chronic treatment with SR58611A resulted also in an increased social interaction time in the social interaction test without affecting motor activity of rats. Furthermore, similarly to diazepam a chronic treatment with the highest doses of SR58611A was followed by increased exploratory behavior in Swiss male mice exposed to the elevated plus maze test. These effects are mediated by beta(3) adrenoceptors since i.p. pretreatment with the selective beta(3) adrenoceptor antagonist SR59230A (5 mg/kg) blocked the effects of SR58611A. Finally, also the 5HT antagonist methysergide (2 mg/kg) prevented the antidepressant and anxiolytic-like activity of SR58611A indicating that 5HT transmission is strictly involved in its action.

*Pharmacol Res.* 2007 Nov;56(5):382-92. Epub 2007 Sep 11.

### **Endocannabinoids and neurodegenerative diseases.**

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The cannabinoid CB1 and CB2 receptors, the endogenous endocannabinoid (EC) ligands anandamide (AEA) and 2-arachidonylethanolamide, and the degradative enzymes fatty acid amide hydrolase (FAAH) and monoglyceride lipase (ML) are key elements of the EC system implicated in different physiological functions including cognition, motor activity and immune responses. Thus, both the possible neuroprotective role of ECs and their modulating action on neurotransmitter systems affected in several neurodegenerative diseases such as Alzheimer's disease (AD),

Huntington's disease (HD) and multiple sclerosis (MS) are currently under investigation. Accumulating data show an unbalance in the EC system (i.e. decrease of neuronal cannabinoid CB1 receptors, increase of glial cannabinoid CB2 receptors and overexpression of FAAH in astrocytes) in experimental models of AD as well as in post-mortem brain tissue of AD patients, suggesting its possible role in inflammatory processes and in neuroprotection. However, the mechanisms of the EC modulation of immune response are not fully understood. By contrast, in HD a reduced EC signaling, given both by the loss of cannabinoid CB1 receptors and decrease of ECs in brain structures involved in movement control as basal ganglia, has been well documented in preclinical and clinical studies. Thus, in the present review we discuss recent data concerning the role of the EC system in the pathophysiology of AD and HD, two neurodegenerative diseases characterized by cognitive deficit and motor impairment, respectively. We focus on the effects of compounds modulating the EC system (agonists/antagonists of cannabinoid CB1 and CB2 receptors, or inhibitors of ECs metabolism processes) on the symptoms and/or progression of neurodegenerative diseases.

*Neuropsychopharmacology.* 2007 Dec;32(12):2511-9. Epub 2007 Mar 14.

### **Chronic antidepressants induce redistribution and differential activation of alphaCaM kinase II between presynaptic compartments.**

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Changes in synaptic plasticity are involved in pathophysiology of depression and in the mechanism of antidepressants. Ca(2+)/calmodulin (CaM) kinase II, a protein kinase involved in synaptic plasticity, has been previously shown to be a target of antidepressants. We previously found that antidepressants activate the kinase in hippocampal neuronal cell bodies by increasing phosphorylation at Thr(286), reduce the kinase phosphorylation in synaptic membranes, and in turn its phosphorylation-dependent interaction with syntaxin-1 and the release of glutamate from hippocampal synaptosomes. Here, we investigated the chronic effect of different antidepressants (fluoxetine, desipramine, and reboxetine) on the expression and function of the kinase in distinct subcellular compartments in order to dissect the different kinase pools affected. Acute treatments did not induce any change in the kinase. In total tissue extracts chronic drug treatments induced activation of the kinase; in hippocampus (HC), but not in prefrontal/frontal cortex, this was partially accounted for by increased Thr(286) phosphorylation, suggesting the involvement of different mechanisms of activation. In synaptosomes, all drugs reduced the kinase phosphorylation, particularly in HC where, upon fractionation of the synaptosomal particulate into synaptic vesicles and membranes, we found that the drugs induced a redistribution and differential activation of the kinase between membranes and vesicles. Furthermore, a large decrease in the level and phosphorylation of synapsin I located at synaptic membranes was consistent with the observed decrease of CaM kinase II. Overall, antidepressants induce a complex pattern of modifications in distinct subcellular compartments; at presynaptic level, these changes are in line with a dampening of glutamate release.

*Curr Med Chem.* 2008;15(24):2420-32.

### **The cell cycle molecules behind neurodegeneration in Alzheimer's disease: perspectives for drug development.**

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Alzheimer's disease (AD), the leading cause of senile dementia, has become a considerable social and economical problem. Current AD therapeutics provide mainly symptomatic short-term be-

nefit, rather than targeting disease mechanisms. The hallmarks for AD are beta-amyloid plaques, neurofibrillary tangles, and regionalized neuronal loss. Additional neuropathological features have been described that may provide some clues to the mechanism by which neurons die in AD. Specifically, the aberrant expression of cell cycle proteins and the presence of de novo-replicated DNA in neurons have been described both in AD brain and in culture models of the disease. The unscheduled cell cycle events are deleterious to neurons, which undergo death rather than complete the cell cycle. Although our understanding of the neuronal cell cycle is not complete, experimental evidence suggests that compounds able of arresting the aberrant cell cycle will yield neuroprotection. This review focuses on drug development centered on the cell cycle hypothesis of AD.

*J Neurosci Res.* 2008 Feb 1;86(2):350-5.

### **Integrins mediate beta-amyloid-induced cell-cycle activation and neuronal death.**

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Early intracellular events responsible for cell-cycle induction by beta-amyloid (A beta) in neurons have not been identified yet. Extracellular signal-regulated kinases 1/2 (ERK1/2) have been identified in this pathway, and inhibition of ERK activity prevents cell-cycle activation and reduces neuronal death induced by A beta. To identify upstream events responsible for ERK activation, attention has been focused on integrins. Treatment of SH-SY5Y cells, differentiated by long-term exposure to 10 microM retinoic acid with a neutralizing anti-alpha1-integrin antibody significantly reduced A beta-induced neuronal death. However, cell-cycle analysis showed that treatment with anti-alpha1-integrin per se produced changes in the distribution of cell populations, thus hampering any effect on A beta-induced cell-cycle activation. 4-Amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazol(3,4-D)pyramide, an inhibitor of src protein kinases that colocalizes with focal adhesion kinase (FAK) and is involved in integrin signaling, was effective in reducing activation of the cell cycle and preventing induction of neuronal death by A beta while inhibiting ERK1/2 phosphorylation. Similar results were obtained when FAK expression was down-regulated by siRNA silencing. The present study identifies a sequence of early events in the toxic effect of A beta in neuronal cultures that involves interaction with integrins, activation of FAK/src, enhanced phosphorylation of ERK1/2, and induction of the cell cycle, all leading to neuronal death.

*Toxicol In Vitro.* 2008 Mar;22(2):541-7. Epub 2007 Oct 14.

### **Expression profile of ErbB receptor's family in human alveolar type 2-like cell line A549 exposed to hexavalent chromium.**

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Occupational exposure to hexavalent chromium (Cr (VI)) compounds is associated with increased risk of pulmonary disease. In the present study we have investigated temporal expression of ErbB's receptors family in A549 cells after exposure to Cr (VI). Treatment with 10 microM or 300 microM of Na<sub>2</sub>CrO<sub>4</sub> induced apoptotic cell death within 24h. Based on data obtained by ELISA cell death detection method and fluorescence microscopy, the concentration of 10 microM was chosen to study the expression of ErbB receptors family. Such concentration reflects a condition of acute toxicity in which cells survived up to 24h. Real time quantitative PCR has been performed to analyze the expression profiles of ErbB family genes following chromium toxicity. The expression of EGFR and ErbB2 receptors was significantly reduced after 1h and 4h of treatment while ErbB2 receptor was significantly increased and EGFR receptor returned to basal value after 24h. Instead, ErbB3 receptor was overexpressed after 1h, returned to basal level after 4h and increased its level after 24h. Exposure to chromium did not change expression level of ErbB4 receptor in A549 cell line. The present data suggests that expression changes

in ErbB receptors might have a role in the carcinogenic effects induced by this pneumotoxic agent.

*Pharmacol Res.* 2008 Apr;57(4):296-302. Epub 2008 Mar 4.

### **Reduced activation of intracellular signaling pathways in rat prefrontal cortex after chronic phen-cyclidine administration.**

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Evidence exists that schizophrenia is characterized by deficits in cell-cell communication and information processing. In the present study, we used the phen-cyclidine (PCP) animal model of schizophrenia to investigate possible defects in intracellular signaling proteins involved in neuroplasticity. Western Blot analysis has been performed to determine total and phospho-protein levels of extracellular signal-regulated kinases 1/2 (ERK1/2), type II calcium/calmodulin-dependent protein kinase (alphaCaMKII) and cAMP-response element binding protein (CREB) in prefrontal cortex (PFC) and hippocampus (HIP) of rat chronically treated with PCP, whereas their mRNA levels were determined by real time RT-PCR. We found reduced levels of P-ERK1/2, P-alpha-CaMKII and P-CREB in prefrontal cortex of PCP-treated animals when compared to controls, whereas no effects were observed on total protein or mRNA levels. Conversely, no significant changes were detected on protein levels or mRNA expression in hippocampus. Given the role of ERK1/2, alphaCaMKII and CREB in neuroplastic mechanisms and cell communication, our data suggest that their decreased activation following chronic PCP administration can contribute to cortical defects occurring in schizophrenia, and may therefore represent potential targets for pharmacological intervention.

*Eur Neuropsychopharmacol.* 2008 Apr;18(4):271-7. Epub 2007 Sep 4.

### **Increased sensitivity to antidepressants of D3 dopamine receptor-deficient mice in the forced swim test (FST).**

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Evidence exists for a dopaminergic system dysregulation in mood disorders. In particular, depression may be accompanied by a relative fall of brain dopamine (DA) availability, while the increase of dopamine D2/D3 receptors (D2R/D3R) binding may reflect a compensatory change following primary reduction of mesolimbic DA levels. It is well established that D3Rs, acting as autoreceptors, inhibit DA synthesis and release, although lack of selective compounds have limited the progress in understanding D3Rs role in mood disorders. Aim of this study was to assess the behavioral responses of D3R-deficient (D3(-/-)) mice tested in the forced swim test (FST) and to evaluate their sensitivity to the treatment with different antidepressant drugs. Different groups of mice received one injection of the tricyclic compound, clomipramine (1, 5 and 10 mg/kg) or of one of the selective serotonin reuptake inhibitors (SSRIs), paroxetine, sertraline or citalopram (1, 4 and 16 mg/kg), 30 min prior the behavioral test. Vehicle-injected wild type (WT) mice and D3(-/-) animals were used as controls and submitted to the same experimental procedure. In a preliminary experiment, vehicle-injected D3(-/-) mice, but not their littermates, failed to show an increased immobility time in FST as compared to intact controls, suggesting an increased resistance to injection-induced stress in the former. Clomipramine 1 mg/kg failed to affect behavioral responses of both D3(-/-) mice and WT animals. After the 5 mg/kg dose, D3(-/-) and WT mice showed a better performance in FST than vehicle-injected controls, with a lower immobility time exhibited by D3(-/-) mice than that shown by WT animals. No difference was found between WT mice treated with the highest dose of clomipramine (10 mg/kg) and the respective controls, although D3(-/-) mice exhibited a decreased immobility time as compared to vehicle-injected controls. In contrast to WT animals, when treated with 1 mg/kg sertraline and the 4 mg/kg dose of every SSRI D3(-/-) mice exhibited a decreased immobility time in FST in comparison to vehicle-injected controls. Further-



more, 16 mg/kg doses of citalopram, paroxetine or sertraline induced a greater reduction of immobility time in D3(-/-) mice than in WT-treated animals as compared to their respective controls. These data suggest that D3(-/-) mice, as being more resistant to stressful procedure than WT littermates, are more sensitive to antidepressants in FST paradigm than the former. Although the present data do not allow any conclusion on the neurochemical base of this difference, it might be possible that the greater sensitivity to antidepressants depends on a higher DA levels in mesolimbic pathways following the lack of D3Rs.

*Neurobiol Dis.* 2008 May;30(2):234-42. Epub 2008 Feb 13.

### **TGF-beta 1 protects against Abeta-neurotoxicity via the phosphatidylinositol-3-kinase pathway.**

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beta-Amyloid (A beta) injection into the rat dorsal hippocampus had a small neurotoxic effect that was amplified by i.c.v. injection of SB431542, a selective inhibitor of transforming growth factor-beta (TGF-beta) receptor. This suggested that TGF-beta acts as a factor limiting A beta toxicity. We examined the neuroprotective activity of TGF-beta1 in pure cultures of rat cortical neurons challenged with A beta. Neuronal death triggered by A beta is known to proceed along an aberrant re-activation of the cell cycle, and involves late beta-catenin degradation and tau hyperphosphorylation. TGF-beta1 was equally protective when added either in combination with, or 6 h after A beta. Co-added TGF-beta1 prevented A beta-induced cell cycle reactivation, whereas later added TGF-beta1 had no effect on the cell cycle, but rescued the late beta-catenin degradation and tau hyperphosphorylation. The phosphatidylinositol-3-kinase (PI-3-K) inhibitor, LY294402, abrogated all effects. Thus, TGF-beta1 blocks the whole cascade of events leading to A beta neurotoxicity by activating the PI-3-K pathway.

*Pharmacol Biochem Behav.* 2008 Sep;90(3):463-9. Epub 2008 Apr 12.

### **Behavioral effects of saredutant, a tachykinin NK2 receptor antagonist, in experimental models of mood disorders under basal and stress-related conditions.**

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The present study was made to investigate the role of tachykinin NK2 receptors in the expression of stress-related behaviors in animals. Under basal conditions, intraperitoneal (i.p.) administration of the selective tachykinin NK2 receptor antagonist, saredutant (1 and 3 mg/kg) or diazepam (1 mg/kg) exerted anxiolytic-like effects in rodents, as they reduced grooming score of Wistar male rats tested in the novelty-induced grooming sampling test (NGT) and increased percentage of time and entries in open arms of Swiss male mice tested in the elevated plus maze (EPM) test. After previous exposure to stress-related conditions, as induced by a 2-min forced swim made 5 min prior to the EPM test, saredutant but not diazepam, exhibited anxiolytic-like effects in mice. To study the antidepressant-like activity of tachykinin NK2 receptor antagonist under basal conditions, different groups of rats were injected i.p. with saredutant (2.5, 5 and 10 mg/kg) or the tricyclic antidepressant, clomipramine (50 mg/kg) and tested in the forced swim test (FST), a widely used antidepressant-responsive test. The influence of stress-related conditions was studied in rats subjected to electric foot-shocks (1 mA, 1 s) 24, 5 and 1 h prior to FST, after drugs injection. In the FST, clomipramine decreased the immobility time only under basal conditions, but not after application of acute foot-shocks. To the contrary, saredutant-treated rats also exhibited more active behavior in FST after previous exposure to stressors. These results give further support to the hypothesis that tachykinin NK2 receptors may be a therapeutic target for pharmacological treatment of stress-related diseases, such as anxiety and depression.

*J Neurochem.* 2008 Nov;107(4):1047-55. Epub 2008 Sep 6.

### **Inhibition of rat glioma cell migration and proliferation by a calix[8]arene scaffold exposing multiple GlcNAc and ureido functionalities.**

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Beta1,4-Galactosyltransferases (beta1,4-GalTase) exposed on the cell surface are involved in cell migration. Specifically, beta1,4-GalTase V is highly expressed in glioma and promotes invasion, growth, and survival of glioma cells. A glycolix[8]arene exposing N-acetylglucosamine (GlcNAc) residues (compound 1) inhibited rat C6 glioma cell migration as assessed in a scratch wound model. This effect was related to inhibition of focal adhesion kinase phosphorylation, measured by western blot analysis, and specifically observed in the area bordering the scratch wound. Compound 1 inhibited also C6 cell proliferation, an effect unrelated to its ability to interact with GalTase as it was mimicked by different calix[8]arene derivatives, all characterized by multivalency and ureido groups. Compound 1 did not induce apoptotic death, but caused a different distribution of C6 cells within the cell cycle. The results here reported identify compound 1 as a molecule able to exert inhibitory effects on C6 cell migration and proliferation, independently, because of distinct components in its structure.

*Brain Res.* 2008 Nov 19;1241:29-35. Epub 2008 Sep 20.

### **PACAP and VIP prevent apoptosis in schwannoma cells.**

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Pituitary adenylate cyclase activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) are structurally endogenous peptides showing rich profile of biological activities. These peptides bind specific membrane receptors belonging to the superfamily of G protein-coupled receptors, the PAC1 and VPAC type receptors. Although these receptors have been identified in oligodendrocytes progenitors cells, to date the effects of PACAP and VIP in Schwann cells are still unknown. In the present study we investigated the expression of these neuropeptides as well as their receptors in a schwannoma cell line. RT-PCR and western blot analysis demonstrated that both PAC1 and VPAC2 receptors, but also PACAP peptide were expressed. To study the physiological effects mediated by PAC1/VPAC receptors, we evaluated their role in preventing apoptotic cell death induced by serum deprivation. Treatment with 100 nM PACAP38 and 100 nM VIP increased survival of serum-deprived schwannoma cells. Anti-apoptotic effects of these peptides were correlated to changes in BCL2 and BAX gene expression. Our results suggested that both PACAP38 and VIP could act as trophic factors in Schwann cells.

*Neurochem Res.* 2008 Dec;33(12):2401-6. Epub 2008 Apr 22.

### **The Wnt antagonist, Dickkopf-1, as a target for the treatment of neurodegenerative disorders.**

Caraci F, Busceti C, Biagioni F, Aronica E, Mastroiacovo F, Cappuccio I, Battaglia G, Bruno V, Caricasole A, Copani A, Nicoletti F.

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The canonical Wnt pathway contributes to the regulation of neuronal survival and homeostasis in the CNS. Recent evidence suggests that an increased expression of Dickkopf-1 (Dkk-1), a secreted protein that negatively modulates the canonical Wnt pathway, is causally related to processes of neurodegeneration in a number of CNS disorders, including Alzheimer's disease (AD), brain ischemia and temporal lobe epilepsy (TLE). Dkk-1 induction precedes neuronal death in cellular and animal models of excitotoxicity, beta-amyloid toxicity, transient global ischemia, and kainate-induced epilepsy. In addition, Dkk-1, which is barely visible in the healthy brain, is strongly induced in brain tissue from AD patients or from patients with TLE associated with hippocampal sclerosis. These data raise the attractive possibility that Dkk-1 antagonists or neutralizing antibodies behave as neuroprotective agents by rescuing the activity of the canonical Wnt pathway.