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Memory Facilitation and Stimulation of Endogenous Nerve Growth Factor Synthesis by the Acetylcholine Releaser PG-9.

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The effects of PG-9, the acetylcholine releaser, on memory processes and nerve growth factor (NGF) synthesis were evaluated. In the mouse passive-avoidance test, PG-9 prevented amnesia induced by both the non selective antimuscarinic drug scopolamine and the M1-selective antagonist S-(-)-ET-126. In the same experimental conditions, PG-9 was also able to prevent antimuscarine-induced amnesia, demonstrating a central localization of the activity. At the highest effective doses, PG-9 did not produce any collateral symptoms as revealed by the Irwin test, and it did not modify spontaneous motility and inspection activity, as revealed by the hole-board test. PG-9 was also able to increase the amount of NGF secreted in vitro by astrocytes in a dose-dependent manner. The maximal NGF contents obtained by PG-9 were 17.6-fold of the control value. The current work indicates the ability of PG-9 to induce beneficial effects on cognitive processes and stimulate activity of NGF synthesis in astroglial cells. Therefore, PG-9 could represent a potential useful drug able to improve the function of impaired cognitive processes.

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Medial Nigral Dopamine Neurons Have Rich Neurotrophin Support in Humans.

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To assess the action of neurotrophin in human dopaminergic neurons, we studied the immunolocalization of neurotrophins or trks in human substantia nigra pars compacta (SNc). The neuromelanin-containing neurons in the SNc showed immunoreactivities for neurotrophins or trks, suggesting an autocrine/paracrine regulation. Quantitative analysis revealed that the percentage of those expressing NGF-like immunoreactivity (NGF-LI), BDNF-LI, NT3-LI, trkA-LI, trkB-LI, or trkC-LI was 66%, 74%, 85%, 66%, 71% or 86%, respectively. The percentage of cells expressing neurotrophins or trks was higher in the medial part than in the lateral part of the SNc. The preferential expression of neurotrophin-trk systems in the medial neurons may, at least partially, explain the differential susceptibility in Parkinson's disease.

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Therapeutic Effects of Aldose Reductase Inhibitor on Experimental Diabetic Neuropathy through Synthesis/Secretion of Nerve Growth Factor.

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We investigated alterations in nerve growth factor (NGF) and ciliary neurotrophic factor (CNTF) contents during treatment with epalrestat, an aldose reductase inhibitor (ARI), on streptozotocin (STZ)-induced diabetic neuropathy in rats. Diabetic rats showed a statistically significant reduction in H-wave-related sensory nerve conduction velocity (HSNCV) and in NGF content in sciatic nerves during the experiment of 8 weeks. No reduction in the CNTF content in sciatic nerves was seen in the diabetic rats. The epalrestat treatment, which started 4 weeks after STZ injection, resulted in a significantly greater NGF content and faster HSNCV than those in untreated diabetic rats. But no statistically significant alterations of motor nerve conduction velocity (MNCV) or CNTF content were seen during the treatment. ARI showed the stimulating effect for NGF synthesis/secretion in rat Schwann cell culture in vitro. These findings suggest that decreased levels of NGF in diabetic sciatic nerves may be involved in the pathogenesis of diabetic neuropathy in these rats and further show that epalrestat treatment can be useful for the treatment of diabetic neuropathy through NGF-induction in Schwann cells and/or inhibition of the polyol pathway.

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Identification of the Three Non-identical Subunits Constituting Human Deoxyribonuclease II.

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We purified DNase II from human liver to apparent homogeneity. The N-terminal amino acid sequences determined for each of three subunits and the previously reported nucleotide sequence suggested that human DNase II was composed of three non-identical subunits, a propeptide, proprotein and mature protein, following a signal peptide. Expression analysis of a series of deletion mutants in COS-7 cells indicated that a single large precursor protein may not be necessary for proteolytic maturation, the propeptide region L17--Q46 may play an essential role in generating the active form of the enzyme.