Catecholamine absorbing proteins (CATNAPs)

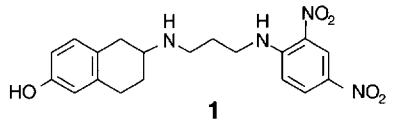
Central dopaminergic systems

The participation of dopaminergic systems in a variety of disorders such as Parkinson's disease and schizophrenia has long been recognized. Many therapeutic compounds prescribed today interact with one of the metabolic enzymes, transporters or receptors that participate in dopaminergic neurotransmission. The heterogeneity of these proteins represents a wealth of molecular targets that can be used for the identification of a new generation of therapeutics. Assay systems for many of these targets adapt perfectly to high-throughput screening techniques, and compound libraries are currently being examined for desirable activities, particularly with respect to receptor specificity.

Over the past decade studies have demonstrated a link between oxidative stress and various disease states. In the central nervous system, where oxygen levels are high, tissues are often sensitive to the toxic products of neurotransmitter oxidation. Dopamine is recognized as one endogenous compound that can be oxidized readily, via enzymatic or non-enzymatic mechanisms, to form highly toxic products. Several of the products of dopamine oxidation (including semiquinone, quinone and free radical species) produce tissue damage similar to that seen in Parkinson's disease and other neurodegenerative disorders. This concept has been highlighted recently in a report by Hastings, T.G., Lewis, D.A. and Zigmond, M.J. [*Proc. Natl. Acad. Sci. U. S. A.* (1996) 93, 1956–1961], who have demonstrated directly the role of oxidation in the toxic effects of striatal dopamine injections.

CATNAPs in the brain

A novel class of brain proteins has been demonstrated to react covalently with dopamine and several structurally related catecholamines. Catechol[CAT]amine[N] absorbing[A] proteins[P] (CATNAPs) are postulated to act as scavenger molecules for the highly toxic products of catecholamine oxidation. It has long been recognized that dopamine has the capacity to react with various protein substrates, but the existence of a specific family of substrate molecules in the brain has been described only recently [Ross, G.M., McCarry, B.E. and Mishra, R.K. *J. Mol. Neurosci.* (1993) 4, 141–148].



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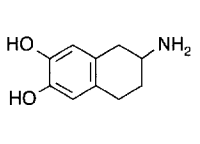
The synthesis of high-specific-activity ligands for CATNAPs, DATN (**1**) and substituted 2-amino-6,7-dihydroxy-tetrahydronaphthalene ADTN (**2**), has been reported by our group. We have explored the ability of various compounds, such as apomorphine **3** and *N*-propylnorapomorphine, to interact with CATNAPs, as well as the ability of reducing agents to prevent the arylation of CATNAPs by DATN [Ross, G.M., McCarry, B.E. and Mishra, R.K. *J. Neurochem.* (1995) 65, 2783–2789]. These proteins have also been demonstrated to respond dramatically to pharmacological manipulation of dopaminergic systems [Modi, P.I. *et al. Eur. J. Pharmacol.* (1996) 299, 213–220].



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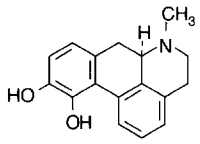

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CATNAP screens

The regulation of CATNAPs, as well as the CATNAP activity of the coming generations of therapeutics, will become an important issue in discovery programs focused on dopaminergic systems. Indeed, the modulation of CATNAP activity directly may provide a key target for the development of drugs aimed at reducing the toxic effects associated with oxidative stress.

Today's challenge for the identification of compounds with CATNAP activity is one of throughput. CATNAPs have previously been characterized by their susceptibility to covalent arylation by radiolabelled ligands, utilizing protein separation and isotope detection methods for visualization. Methods for characterizing radiolabelled proteins such as traditional electrophoresis and autoradiography techniques do not generally lend themselves to large numbers of samples. In the future, implementing assay systems for CATNAPs will require considerable creativity. Fortunately, the development of instrumentation for resolving and detecting large numbers of high-molecular-weight species is making rapid progress. Equipment such as high-throughput gel electrophoresis and multichannel capillary-zone electrophoresis (CE) systems capable of processing high numbers of derivatized proteins are now available.

The identification of these new players in central dopaminergic function coupled with appropriate assay systems will undoubtedly make CATNAPs an important molecular target for consideration within relevant discovery programs.

Gregory M. Ross
Departments of Medicine and Pharmacology & Toxicology
Queen's University, Kingston, Ontario, Canada K7L 2V7
e-mail: rossg@post.queensu.ca

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1359-6446/97/$17.00