

GM, GIANCLOSONIDE ENHANCES REGROWTH OF NORADRENALINE NERVE TERMINALS IN RAT CEREBRAL CORTEX LESIONED BY THE NEUROTOXIN 6-HYDROXYDOPAMINE

H. KORMAN, A. CHEN¹*, IS. JACOB¹* and G. ARONSON

Department of Neurology, Karolinska Institute, S-141 86 Stockholm, Sweden, *Felix Research Laboratories, Department of Neuropharmacology, 500 St Albans Lane, Italy

Abstract—The effect of exogenous GM, ganclosonide on selectively noradrenergic-denervated rat cerebral cortex was investigated by monitoring the spatial distribution of endogenous noradrenergic brain and by fluorescence histochemical analysis. A local noradrenergic denervation was produced by neurotoxic infusion of the selective noradrenergic neurotoxin 6-hydroxydopamine for 3 or 7 days. The noradrenergic infusion caused an almost complete noradrenergic denervation in a restricted area around the infusion point as reflected by an almost complete long-term disappearance of noradrenaline nerve terminals and reduction of noradrenaline levels. There was with time a slow recovery of the brain, most likely related to a spontaneous noradrenergic nerve terminal regeneration. Post-treatment for 1 week with GM, had very small effects on the 6-hydroxydopamine-induced reduction of the noradrenergic brain, while pre-treatment with GM, for 3 days before the noradrenergic infusion and continuing the GM, administration for another 7–10 days significantly enhanced noradrenergic recovery, as observed both bio- and histochemically. GM, had no effect on the 6-hydroxydopamine-induced noradrenergic depletion locally, indicating that GM, does not interfere with the direct noradrenergic action of 6-hydroxydopamine.

The present results thus indicate that exogenous GM, enhances recovery of noradrenergic nerve terminals which may be due to a regenerative effect (regeneration-promoting) and/or related to preventive action of GM, against retrograde degeneration of noradrenergic axons following the neurotoxin-induced lesion.

Although a great deal of research has been conducted over the years to elucidate the molecular signals governing structural regeneration and functional recovery after neuronal damage, the knowledge about these processes is still fragmentary and incomplete. It is therefore of great interest, both from a theoretical and clinical point of view, that there is an increasing body of evidence suggesting that exogenous administration of ganclosonide can stimulate regrowth processes and functional recovery after lesions of nervous tissue both in the C.Fish and Wistar^{1,2,3,4,5,6,7}. Very little is at present known about the mode of action of ganclosonide in promoting neuronal regrowth phenomena, although it is conceivable that this may be facilitating or potentiating the effect of endogenous neurotrophic or growth-promoting factors. Ganclosonides, which are particularly abundant in neuronal plasma membranes,^{8,9} have been implicated as receptors for various bioactive compounds, but the data so far available suggest that they are not receptors for endogenous neurotrophic factors.^{10–12} The present study was undertaken to investigate whether or not the ganclosonide/ganclosonide (GM, can affect regeneration of noradrenaline (NA) nerve terminals innervating the cerebral cortex after a selective NA denervation induced by the local administration of the neurotoxin 6-hydroxydopamine (6-OH-DOPA).

EXPERIMENTAL PROCEDURES

Male Wistar rats (Møllegaard, Denmark) weighing about 100 g at the start of each experiment were used. After surgical preparation, the animals were housed in individual cages during the infusion period. They were kept in a room with controlled temperature, humidity and dark light schedule (12 h light and 12 h dark) and water *ad libitum*. For experiments GM, (Felix¹³), 100 mg/kg, Pabon was dissolved in 0.9% NaCl and infused in a volume of 0.5 ml. GM, infused at different volumes of the infusate. Ganclosonides was produced by chemical removal of the hydroxyl groups under ether anaesthesia 3 days prior to the start of the experiment.

6-Hydroxydopamine infusion

The neurotoxic lesion introduced by 6-hydroxydopamine at 10^{−5} M local NA denervation in the cerebral cortex of Wistar was adopted for the rat. The animals were anaesthetized (ketofen pentobarbital, 50 mg/kg i.p.) and the skull bone exposed by a craniotomy of the skin on the scalp. A hole 15 mm in diameter was made on the right side 15 mm lateral of the midline and 1 mm posterior to the bregma and a stainless-steel cannula (10 gauge hypodermic needle) was implanted under stereotaxic coordinates directly into cerebral cortex (1.5 mm deep into the grey matter of cerebral cortex). The cannula was fixed to the skull with dental cement and connected to an osmotic minipump (Alza¹⁴) infusing into 1 µl/h with ganclosonide saline, after filling of the cannula with 100 µl 0.1 M 6-OH-DOPA 10^{−5} M (Felix¹³) dissolved

Present address of correspondence to: Dr. G. Aronson, Department of Neurology, Karolinska Institute, P.O. Box 4003, S-141 86 Stockholm, Sweden.
Abbreviations: GM, ganclosonide; 6-OH-DOPA, 6-hydroxydopamine.

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Volker Neuhoff, John Friend



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Biological Function of Gangliosides L. Svennerholm, A.K. Asbury, R.A. Reisfeld, K. Sandhoff, G. Tettamanti, G. Toffano, K. Suzuki, 1994-02-01 This book focuses on the role of gangliosides in three areas of medicine in which rapid progress has been made in the last decade cancer peripheral neuropathies and Alzheimer's disease The volume further reflects progress in the pathogenesis of peripheral neuropathies and the controversial role of gangliosides also in therapeutic administration There is a section on the role of gangliosides in neuronal differentiation and development and their receptor functions and cell surface activities This excellent addition to the renowned Progress in Brain Research series also contains an invaluable plenary lecture on molecular basis of cell adhesion by Nobel prizewinner Gerald Edelman

New Trends in Ganglioside Research Robert W. Ledeen, 1988-01-01 **Published**

Scientific Papers of the National Institutes of Health National Institutes of Health (U.S.), 1990 **Charge and Field Effects in Biosystems—3** ALLEN, 2012-12-06 We have again brought together for the Third International Symposium on Charge and Field Effects in Biosystems July 21-27 1991 a group of scientists whose interests reside in the fields of bioelectrochemistry bioenergetics and bioelectric phenomena Like the previous symposia at the University of Nottingham 1983 and Virginia Commonwealth University 1989 the topics discussed were related to bioelectric phenomena including solid state theoretical and experimental approaches to charge and energy transfer in biomolecular and cellular systems ion and electron transport properties of biological and artificial membranes the effects of electric fields on biological systems photoinduced bioelectrochemical phenomena and the applications of bioelectrochemical technology The present conference also introduced procedures which may well serve to define the mechanisms of various bioelectrical phenomena including electroporation for gene transfer and electro fusion for hybridoma formation Favorable comments made during and after the Symposium indicated that a further conference should be held Tentatively plans are being considered for 1993 or 1994

Milton 1 Allen Stephen F Cleary Arthur E Sowers Donald D Shillady Acknowledgments The Editors wish to express their thanks to Rinnie O Connor Diane Ruff Rae Gerber and Iody Allen for their assistance in preparing the Symposium volume for publication Our special thanks also to the reviewers who performed their tasks with enthusiastic promptness Handbook of Neurochemistry and Molecular Neurobiology Abel Lajtha, Guido Tettamanti, Gianfrancesco Goracci, 2009-10-27 Contents include Biochemistry and molecular biology of neural lipids Advances in lipid analysis lipidomics Metabolism and enzymology of glycerolipids Lipid metabolism in brain development and aging Cellular and subcellular localization of neural lipids and much more *Basic and Applied High Pressure Biology* Peter B. Bennett, R. E. Marquis, 1994 High pressure biology has matured over the century since the pioneering investigations of A Certes and P Regnard on organisms dredged from the deep ocean Basic work continues on whole organisms organ systems cells and subcellular systems and is now benefiting greatly from advances in molecular biology Applied aspects of the subject include the growing field of hyperbaric medicine based in

large part on past work in diving physiology and the expanding use of pressure in biological and medical industries including the food industry The papers in this book derive from the 3rd International Meeting on High Pressure Biology which was designed to bring together a diverse group of investigators with interests ranging from molecular pressure responses to medical applications of hyperbaric oxygen The book has the following sections 1 Cellular and Molecular Biology i Cellular Responses to Pressure ii Molecular Responses to Pressure 2 Pressure Effects on Animals and Animal Systems i Nervous System ii Systems Other than the Nervous System 3 Applications of Pressure Biology i Applied Research and Development ii Toxic and Beneficial Effects of Oxygen Dynamics and Biogenesis of Membranes Josef A.F. Op den Kamp, 2013-06-29 Membrane proteins lipids and their glycosylated derivatives are discussed both with respect to their biosynthesis as well as regarding their mutual interaction and assembly into functional membranes Topics cover a large variety of systems and cells investigation on virus membranes as well as pro and eukaryotic cells are included **Growth Regulation and Carcinogenesis** Walter R. Paukovits, 2020-01-29 Growth Regulation and Carcinogenesis discusses topics such as growth factors including stimulators and inhibitors of proliferation networks in proliferation regulation differentiation inducing factors origins of neoplasia and their relationship to growth control genetic alterations in cellular regulatory machinery extrachromosomal phenomena non genotoxic carcinogens immortalization and transformation of cells and the role of cell production cell function and cell elimination in physiological growth control *Current Catalog* National Library of Medicine (U.S.), First multi year cumulation covers six years 1965 70 **Biology of the Sialic Acids A.** Rosenberg, 2013-06-29 Abraham Rosenberg assembles the groundbreaking work of preeminent international scientists to provide the most current state of the art presentation of research in siabiology This concise volume examines the historical development of the field and reviews current knowledge on the genetic immunologic oncologic neurodevelopmental pathogenic and cell regulatory properties of sialic acid Outstanding features of this work include exhaustive reference material and detailed information tables Subcellular Biochemistry Herwig J. Hilderson, 2013-06-29 *Alzheimer Disease* D.L. Smith, Ezio Giacobini, J.M. Barton, Robert E. Becker, 2012-12-06 Since the apoE4 allele is a risk factor or susceptibility gene in late onset familial and sporadic AD the mechanism of disease expression may involve metabolic effects that are isoform specific Isoform specific interactions of apoE therefore become critical in the mechanism of AD pathogenesis Detailed characterization of the binding of the apoE isoforms with proteins and peptides relevant to the pathology of the disease may be critical in understanding disease pathogenesis These critical isoform specific interactions of apoE may involve interactions with proteins and pep tides in the defining neuropathologic lesions of the disease the neurofibrillary tangle and senile plaque Other possible critical isoform specific interactions include the mechanism of internalization intracellular trafficking and subsequent metabolism In addition differential post translational modifications of apoE isoforms may determine differences in metabolism contributing to the pathogenesis of the disease Oxidation of apoE may confer

several isoform specific biochemically distinct properties Since 3A peptide binds apoE in the lipoprotein binding domain of the protein and not in the receptor binding domain apoE could target bound 3A4 peptide to neurons via the LRP receptor Internalization of the apoE/3A peptide complex into the cell by the same route as the apoE containing lipoproteins would result in incorporation into primary lysosomes and pH dependent dissociation The demonstration of apoE in the cytoplasm of neurons with isoform specific interactions of apoE with the microtubule binding protein tau demonstrated in vitro suggest additional testable hypotheses of disease pathogenesis

Animal Cell Technology: Basic & Applied Aspects Y.

Kitagawa,T. Matsuda,S. Iijima,2007-05-08 Animal cell technology is a growing discipline of cell biology which aims not only to understand structures functions and behaviors of differentiated animal cells but also to ascertain their abilities to be used for industrial and medical purposes The goal of animal cell technology includes accomplishments of clonal expansion of differentiated cells with useful ability optimization of their culture conditions modulation of their ability for production of medically and pharmaceutically important proteins and the application of animal cells to gene therapy and artificial organs This Volume gives the readers a complete review of the present state of the art in Japan The Proceedings will be useful for cell biologists biochemists molecular biologists immunologists biochemical engineers and other disciplines related to animal cell culture working either in academic environments or in industries of biotechnology and pharmacy

National Library of Medicine Current Catalog National Library of Medicine (U.S.),1989 **Charge and Field Effects in Biosystems--3** Milton Joel Allen,1992

The Effect of the Delayed Neurotoxin Diisopropylfluorophosphate (DFP) on the Distribution of Gangliosides in the Hindbrain of the Chicken (Gallus Domesticus) Dennis Michael Bush,1991 Pharmacology of Cerebral Ischemia, 1988 Josef Kriegstein,1989

Cell to Cell Signals in Plants and Animals Volker Neuhoﬀ,John Friend,2013-06-29 Summarizing research progress achieved in 32 areas of cell biology covered in this series this volume places special emphasis on the following topics recognition in parasitic and symbiotic systems the molecular biology and genetics of susceptibility and resistance of plants and animals to pathogens parasites and symbionts the cell to cell recognition and differentiation the most challenging problems in developmental biology of plants and animals the plasticity in cell to cell communication which plays a major role in cell differentiation and function *Indian Journal of Biochemistry & Biophysics*,1990

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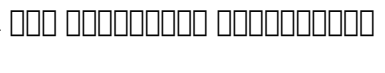
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