An alternative amino-terminus expressed in the central nervous system converts agrin to a type II transmembrane protein

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 155374
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Year 2001
Title An alternative amino-terminus expressed in the central nervous system converts agrin to a type II transmembrane protein
Journal Molecular and cellular neuroscience
Volume 17
Number 1
Pages / **Article-Number** 208-225
Keywords Agrin/genetics/*metabolism; Animals; Cell Line; Cell Membrane/*metabolism; Central Nervous System/*metabolism; Chick Embryo; Conserved Sequence/physiology; Glycosylation; Humans; Membrane Proteins/*biosynthesis; Mice; Neuromuscular Junction/metabolism; Protein Processing; Post-Translational/genetics; Protein Sorting Signals/genetics/*physiology; Rats; Receptor Aggregation/physiology; Receptors; Cholinergic/metabolism; Sequence Homology; Amino Acid; Species Specificity; Transfection
Agrin is a basal lamina-associated heparansulfate proteoglycan that is a key molecule in the formation of the vertebrate neuromuscular junction. The carboxy-terminal part of agrin is involved in its synaptogenic activity. The amino-terminal end of chick agrin consists of a signal sequence, required for the targeting of the protein to the secretory pathway, and the amino-terminal agrin (NtA) domain that binds to basal lamina-associated laminins. The cDNA encoding rat agrin lacks this NtA domain and instead codes for a shorter amino-terminal end. While the NtA domain is conserved in several species, including human, sequences homologous to the amino-terminus of rat agrin have not been described. In this work, we have characterized these amino-terminal sequences in mouse and chick. We show that they all serve as a noncleaved signal anchor that immobilizes the protein in a N(cyto)/C(exo) orientation in the plasma membrane. Like the secreted form, this transmembrane form of agrin is highly glycosylated indicative of a heparansulfate proteoglycan. The structure of the 5' end of the mouse agrin gene suggests that a distinct promoter drives expression of the transmembrane form. Agrin transcripts encoding this form are enriched in the embryonic brain, particularly in neurons. To our knowledge, this is the first example of a molecule that is synthesized both as a basal lamina and a plasma membrane protein.
Publisher Elsevier
ISSN/ISBN 1044-7431
edoc-URL http://edoc.unibas.ch/dok/A5258408
Full Text on edoc Restricted;
Digital Object Identifier DOI 10.1006/mcne.2000.0932
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/11161480
ISI-Number WOS:000166683900016
Document type (ISI) Article