A neuronal inhibitory domain in the N-terminal half of agrin

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 155368
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Year 2002
Title A neuronal inhibitory domain in the N-terminal half of agrin
Journal Journal of Neurobiology
Volume 50
Number 2
Pages / **Article-Number** 164-179
Keywords agrin, neurite outgrowth, integrins, NCAMs, motor neurons
Agrin is required for appropriate pre- and postsynaptic differentiation of neuromuscular junctions. While agrin's ability to orchestrate postsynaptic differentiation is well documented, more recent experiments have suggested that agrin is also a "stop signal" for the presynaptic neuron, and that agrin has actions on neurons in the CNS. To elucidate the neuronal activities of agrin and to define the receptor(s) responsible for these functions, we have examined adhesions of neurons and their neurite-outgrowth responses to purified agrin in vitro. We find that both full-length agrin and the C-terminal 95 kDa of agrin (agrin c95), which is sufficient to induce postsynaptic differentiation, are adhesive for chick ciliary ganglion (CG) and forebrain neurons. Consistent with previous findings, our results show that N-CAM binds to full-length agrin, and suggest that alpha-dystroglycan is a neuronal receptor for agrin c95. In neurite outgrowth assays, full-length agrin inhibited both laminin- and N-cadherin-induced neurite growth from CG neurons. The N-terminal 150 kDa fragment of agrin, but not agrin c95, inhibited neurite outgrowth, indicating that domains in the N-terminal portion of agrin are sufficient for this function. Adhesion assays using protein-coated beads and agrin-expressing cells revealed differential interactions of agrin with members of the immunoglobulin superfamily of cell adhesion molecules. However, none of these, including N-CAM, appeared to be critical for neuronal adhesion. In summary, our results suggest that the N-terminal half of agrin is involved in agrin's ability to inhibit neurite outgrowth. Our results further suggest that neither alpha-dystroglycan nor N-CAM, two known binding proteins for agrin, mediate this effect.
Publisher Wiley
ISSN/ISBN 0022-3034 ; 1090-2104
edoc-URL http://edoc.unibas.ch/dok/A5258402
Full Text on edoc No;
Digital Object Identifier DOI 10.1002/neu.10025
ISI-Number WOS:000173487200007
Document type (ISI) Article