An amino-terminal extension is required for the secretion of chick agrin and its binding to extracellular matrix

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Agrin is an extracellular matrix (ECM) protein with a calculated relative molecular mass of more than 200 kD that induces the aggregation of acetylcholine receptors (AChRs) at the neuromuscular junction. This activity has been mapped to its COOH terminus. In an attempt to identify the functions of the NH2-terminal end, we have now characterized full-length chick agrin. We show that chick agrin encoded by a previously described cDNA is not secreted from transfected cells. Secretion is achieved with a construct that includes an additional 350 bp derived from the 5' end of chick agrin mRNA. Recombinant agrin is a heparan sulfate proteoglycan (HSPG) of more than 400 kD with glycosaminoglycan side chains attached only to the NH2-terminal half. Endogenous agrin in tissue homogenates also has an apparent molecular mass of >400 kD. While the amino acid sequence encoded by the 350-bp extension has no homology to published rat agrin, it includes a stretch of 15 amino acids that is 80% identical to a previously identified bovine HSPG. The extension is required for binding of agrin to ECM. AChR aggregates induced by recombinant agrin that includes the extension are considerably smaller than those induced by agrin fragments, suggesting that binding of agrin to ECM modulates the size of receptor clusters. In addition, we found a site encoding seven amino acids at the NH2-terminal end of agrin that is alternatively spliced. While motor neurons express the splice variant with the seven amino acid long insert, muscle cells mainly synthesize isoforms that lack this insert. In conclusion, the cDNAs described here code for chick agrin that has all the characteristics previously allocated to endogenous agrin.

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