Alternative splicing of agrin alters its binding to heparin, dystroglycan, and the putative agrin receptor

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Agrin is a heparan sulfate proteoglycan that induces aggregation of acetylcholine receptors (AChRs) at the neuromuscular synapse. This aggregating activity is modulated by alternative splicing. Here, we compared binding of agrin isoforms to heparin, alpha-dystroglycan, and cultured myotubes. We find that the alternatively spliced 4 amino acids insert (KSRK) is required for heparin binding. The binding affinity of agrin isoforms to alpha-dystroglycan correlates neither with binding to heparin nor with their AChR-aggregating activities. Moreover, the minimal fragment sufficient to induce AChR aggregation does not bind to alpha-dystroglycan. Nevertheless, this fragment still binds to cultured muscle cells. Its binding is completed only by agrin isoforms that are active in AChR aggregation, and therefore this binding site is likely to represent the receptor that initiates AChR clustering.

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