# Activation of muscle-specific receptor tyrosine kinase and binding to dystroglycan are regulated by alternative mRNA splicing of agrin

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Agrin induces the aggregation of postsynaptic proteins at the neuromuscular junction (NMJ). This activity requires the receptor-tyrosine kinase MuSK. Agrin isoforms differ in short amino acid stretches at two sites, called A and B, that are localized in the two most C-terminal laminin G (LG) domains. Importantly, agrin isoforms greatly differ in their activities of inducing MuSK phosphorylation and of binding to alpha-dystroglycan. By using site-directed mutagenesis, we characterized the amino acids important for these activities of agrin. We find that the conserved tripeptide asparagineglutamate-isoleucine in the eight-amino acid long insert at the B-site is necessary and sufficient for full MuSK phosphorylation activity. However, even if all eight amino acids were replaced by alanines, this agrin mutant still has significantly higher MuSK phosphorylation activity than the splice version lacking any insert. We also show that binding to alpha-dystroglycan requires at least two LG domains and that amino acid inserts at the A and the B splice sites negatively affect binding.

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