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Spadin and its Analogs: A new concept in antidepressant drug design

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From the posttranslational maturation process of sortilin, we identified a 17 amino acid peptide, called spadin as a new antidepressant drug concept. Spadin exerts its antidepressant actions on the TREK-1 potassium channel, a novel antidepressant (AD) target. We showed that spadin acts more rapidly in comparison to other ADs. We have pointed out that spadin induced neurogenesis after only 4-day treatments. We demonstrated that spadin did not display side effects at the cardiac level and on TREK-1 controlled functions such as stroke, epilepsy or pain. With the final goal to make spadin a drug for human clinic, we sought analogs of spadin demonstrating a better affinity or a better in vivo stability or both. By electrophysiology on HEK293 cells stably transfected with TREK-1 channels, several analogs were tested for their ability to block the TREK-1 channel activity. AD effects were measured by using the forced swim and novelty suppressed feeding tests. Synaptogenesis was investigated by measuring the expression level of the synaptic protein PSD-95 in *in vitro* cultured neurons. Our data allow us to identify a shortened spadin, called mini-spadin, that displayed the same AD properties as spadin and a 400 fold increase in the TREK-1 affinity. Mini-spadin increased the synaptogenesis marker PSD95 levels after only 24 hours of treatment, suggesting that like spadin, mini-spadin was able to induce neurogenesis and synaptogenesis. Even if further experiments are required, the mini-spadin appears to be more efficient than spadin offering a very promising alternate to spadin as human drug.

Biography

Marc Borsotto has obtained his PhD in the University of Nice Côte d'Azur. He is a Researcher Director (CNRS) at the Institut de Pharmacologie Moléculaire et Cellulaire (Valbonne, France), he is the PI of the project "Spadin and Depression". His laboratory is member of the ICST Excellence Network, a connection between ionic channels research teams. He is internationally recognized in the field of potassium channels (ATP-sensitive K^+ channels, KCNQ2/3 K^+ channels and Two-pore domain K^+ channels). He published more than 50 articles cited more than 2600 fold, h-index = 25, i10 = 34 (Google scholar). He is coauthor of 4 patents.

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