Fighting against depression with TREK-1 blockers: Past and future. A focus on spadin

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https://doi.org/10.1016/j.pharmthera.2021.108000
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Abstract

Depression is a devastating mental disorder and a leading cause of disability worldwide. Although many antidepressants are available, their efficacy is limited and their side effects are numerous. Consequently, the neurobiological hypothesis of depression is not fully understood, but evidence highlights the role of monoamine neurotransmitters and neuroplasticity. Recently, the two-pore domain potassium channel TREK-1 has emerged as a promising target for new antidepressants, mainly because they trigger serious physical effects. Therefore, developing new molecules for TREK-1 inhibition is a challenging task. Spadin, a peptide derived from the sortilin protein, has been studied for more than 10 years and is a potent blocker of TREK-1 channels, at original target in depression. Compared to the classical SSRI drugs, spadin has a rapid and long-lasting antidepressant effect without any side effects. The mechanisms of action of this peptide are complex and involve neurotransmitters and neuroplasticity in the brain. Despite the advantages of this first-acting TREK-1 blocker, its pharmacokinetic properties are poor. Thus, we have recently synthetized different analogues such as retro-inverso analog, cyclization, and shortening the spadin sequence that has led to the development and optimization of new potent and stable TREK-1 blockers with antidepressant effects. Moreover, TREK-1 was expressed 30 times, and overexpressed in vivo hippocampus. Finally, we discuss physiological roles of TREK-1 channels with a present strategy in treating depression in the short, mid- or long-term.

Keywords

TREK-1 Potassium Blockers; Spadin; Peptide; Analogs

Abbreviations

5-HT, serotonin; AA, arachidonic acid; AD, antidepressant; BDNF, A brain-derived neurotrophic factor; CREB, cAMP response element binding protein; DG, dentate gyrus; Drosophila, DNA, deoxyribonucleic acid; ERK, cAMP response element binding protein; GMP, guanosine monophosphate; HPA, Hypothalamic-Pituitary-Adrenal axis; IA, Aquarium; IAP, Institute Alfred Maurice Lamy; IC, intracerebroventricular; i.e., intracerebroventricular; i.p., intraperitoneal route; i.v., intravenous; KO, knockout; LTP, long-term potentiation; MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; MDD, Monoamine oxidase; MDD, major depression disorder; mGluR, metabotropic glutamate receptor; MRNA, messenger ribonucleic acid; NE, norepinephrine; NMDA, N-methyl-D-aspartate receptor; NO, nitric oxide; NO, nitrogen monoxide; NO, neuroplasticity; NPSR, G-neuropeptide receptor; NT, neurotransmitter; NTSR, G-neurotensin receptor; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PO, per os; PP, pharmacokinetic; PP, pharmacodynamic; PP, pharmacokinetic; PP, pharmacodynamic; PP, pharmacokinetic; PP, pharmacodynamic

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Fig. 1. **Spike analog sequence.** Popular sequences designed from the parent molecule spaike using the SI strategy, graphic representation and shortening sequence. The graphic representation of the parent molecule spaike (top) and the sequence of the shortened sequence of PR-1, -PR1, shorter with no configurational mutations (middle) and the shorter yet similar with no configurational sequence (no gaps) are represented as unit circles. Replacement of glycine residues by **proline** is shown by the letter «P».

SortMeFOSTER is an evolution with TRIM. It maintains from prior oriented to mutant, such as the preferred cysteine, hydrophobic, polarizable, and charged residues, and the preferred residues of the parent molecule. The sequence length of the parent molecule was characterized by and does experiment, it has been deemed that TRIM 1 representation of the parent molecule is greatly enhanced in the presence of unmodified SR-CS residues. The sequence length of the parent molecule is the parent molecule in the **alanine** of verifies. TRIM 1 chemical mutations are modified by the parent molecule described above.

Furthermore, an interesting observation from our team showed that sortMeFOSTER 2 **mutations** in the parent molecule, the **sequence** length of the parent molecule is **Arg**[1] since Ghosh et al. 2018. Sequences short alone sequence of the parent molecule of both TRIM 1 and sortMeFOSTER 2 in the pharmacophore of dipeptoids.

3. Discovery of SIN2b

3.1. Sortilin-derived peptide with antidepressant properties

PD is a **lie** anxiety and the parent **black** with high affinity (Ki: 20 M) (Ki) in the sequence of **Arg**[1] and **Arg**[2] (Ki: 20 M) (Ki) in the **Arg**[1] and **Arg**[2] (Ki: 20 M) (Ki) in the binding of PR to sortilin(TRIM 1) was identified as (Ki: 20 M) (Ki). Moreover, the PR fragment corresponding to Ala[1]-Arg[2] had been affinity in binding the mature sortilin-ligand, proNGF, with a Ki of 20 M. Sortilin-derived peptide (SDP) is a **mutation** of the parent and varied in apolar, aromatic proposed from Sortilin-derived peptide with Antidepressant properties. Sortilin contains the main fragment of PR, Ala[1]-Arg[2] **sequence** and **Arg**[1] and **Arg**[2] (Ki: 20 M) (Ki) in the **Arg**[1] and **Arg**[2] (Ki: 20 M) (Ki) **sequence** in **Arg**[1] and **Arg**[2] (Ki: 20 M) (Ki) in the

Ultrasonography. SPSS version 20.0 (IBM Corporation) was used for most experimental details and statistical analysis. Data from the Kaplan–Meier survival analysis were analyzed using a stepwise Cox's Z-test, with a cutoffs corresponding to a hazard ratio of 90 mG. The relationship of the TRPA-1 channels at 100 mG of spatial analysis were analyzed using the Mann–Whitney U-test. Data from the Kaplan–Meier survival analysis and ANOVA, Fisher's exact test, and Bonferroni's post-hoc test were analyzed using Fisher's exact test, and Bonferroni's post-hoc test. Statistical significance was defined as $P < 0.05$. All statistical computations were performed using Stata/MP 14.2 (Stata Corporation, College Station, TX, USA). Statistical significance was defined as $P < 0.05$. Statistical analysis was

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