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**An investigation of relaxin-3 stapled peptides as novel agents for the treatment of feeding and neuropsychiatric disorders****Subhi Marwari**

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**R**elaxin-3, the most recently identified member of the relaxin-insulin family of peptides, is mainly expressed as a neuropeptide in the brain where its cognate receptor is relaxin/insulin-like family peptide receptor 3 (RXFP3). The brain stem nucleus incertus (NI) is the capital source of relaxin-3 which projects widely to midbrain and forebrain structures implicating the roles of relaxin-3/RXFP3 nexus in metabolism, arousal, stress and memory suggesting novel targets for the treatment of neuropsychiatric disorders. However, basic preclinical research has been limited by the lack of tools to target RXFP3 as experimental ligands for understanding the basic biological functions of NI and relaxin-3. Currently, the best agonists and antagonists for RXFP3 are, respectively, human relaxin-3 and R3(BΔ23-27)R/I5, a chimera between a truncated relaxin-3 B-chain and A-chain of another member of the insulin/relaxin family. These large peptides do not transverse the blood-brain barrier (BBB) and so have to be infused directly into the brain which are unlikely to be amenable to development as drugs due to issues with stability in vivo and brain penetration. Stapling of peptides, in which peptides are chemically stabilized by covalently crosslinking the side-chains of two amino acids leading into well-defined bioactive  $\alpha$ -helical conformation, has been proposed as a breakthrough solution to address important yet currently undruggable targets. In the present study, we have stapled the relaxin-3 B-chain at 14s18, 18s22 (i+4) positions and alternate stapling positions which has allowed the generation of smaller RXFP3 ligands with increased  $\alpha$ -helicity and resistance to proteolysis and in the present study, for the first time we have also reported that the stapling of human relaxin-3 B-chain enhances the biological activity. A designed series of stapled relaxin-3 B-chain peptides has been tested in the in vitro and in vivo assays of RXFP3 receptor binding/activation and behavioral effects. Compounds with promising profiles will be further tested for in vivo efficacy testing in rats for monitoring of feeding and anxiety behaviors leading towards potential new avenues for neuropsychiatric drugs.

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