NEUROIMMUNE ASPECTS OF MOOD, ANXIETY AND COGNITIVE EFFECTS OF LEADS/DRUG CANDIDATES ACTING AT GABAA AND/OR SIGMA-2 RECEPTORS: IN VITRO/IN VIVO DELINEATION BY NANO- AND HIPSC-BASED PLATFORMS

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Mood, anxiety and cognitive symptoms in psychiatry and neurology represent a significant worldwide burden. Due to difficulties in disease modeling and drug delivering to the site of action, as well as gaps in in vitro/in vivo extrapolation, the efforts to elucidate the roles of stress and neuroimmune pathways in both, etiology and therapy of these symptoms are challenging, but may nevertheless result in novel mechanisms of action. Recent preclinical studies provided novel leads/drug candidates with promising mood, anxiety and cognitive effects, the intellectual property rights of which are co-owned by the project beneficiary. We aim to: (1) incorporate the selective ligands of GABAA and/or sigma-2 receptors, with code names GL-II-73, DK-I-56, MM-I-03 and CW-02-79, together with two reference sigma-2 receptor ligands (siramesine and RHM-1), into the optimized nanoparticles and target their delivery to the human induced pluripotent stem cell (hiPSC)-based tri-culture cell neuroinflammation model, or rat brain; (2) quantify the immunological/morphological/neurochemical markers in immunologically challenged hiPSC-derived neurons, astrocytes and glia cells, and (3) assess their effects on behavior and biological markers in immunologically challenged animals of both sexes subjected to chronic mild unpredictable stress. We assume that the targeted nanodelivery of selected compounds to the brain will improve their pharmacokinetic profile, fortify their beneficial effect on mood, anxiety and cognition, and help delineate the contributing neuroimmune effects presumably arising mainly from microglia. The familiarization with neuroimmune aspects and pharmacokinetic optimization will support the preclinical progress of these compounds and might provide a rationale for designing clinical trials.

References

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NEUROIMUNSKI ASPEKTI EFEKATA VODEĆIH JEDINJENJA/LEKOVA KANDIDATA KOJI DELUJU PREKO GABAA I/ILI SIGMA-2 RECEPTORA NA RASPOLOŽENJE, ANKSIOZNOST I KOGNICIJU: IN VITRO/IN VIVO DELINEACIJA PRIMENOM NANO- I HIPSC PLATFORMI

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Raspoloženje, anksioznost i kognitivni simptomi u psihijatriji i neurologiji predstavljaju značajno opterećenje za zdravstvene sisteme na globalnom nivou. Usled poteškoća u modelovanju bolesti i isporuci lekova na mesto delovanja, kao i jaza u *in vitro/in vivo* ekstrapolaciji, potreba da se osvetle uloge stresa i neuroimunskih puteva u etiologiji i terapiji ovih simptoma je izazov, i može rezultovati u novim mehanizmima delovanja. Nedavne prekliničke studije obezbedile su nova vodeća jedinjenja/lekove kandidate sa obećavajućim efektima na raspoloženje, anksioznost i kogniciju, rezultujući prihvatanjem patentnih prava čiji je suvlasnik predlagač projekta. Cilj projekta je da: (1) inkorporiramo ligande selektivne za GABAA i/ili sigma-2 receptore, sa kodiranim imenima GL-II-73, DK-I-56, MM-I-03 i CW-02-79, zajedno sa dva referentna liganda za sigma-2 receptore (siramesin i RHM-1), u optimizovane nanočestice i da omogućimo njihovu ciljnu isporuku u hiPSC-bazirani trićelijski model neuroinflamacije, ili mozak pacova; (2) kvantifikujemo imunološke/morfološke/neurohemijske markere u imunološki izazvanim hiPSC-derivisanim neuronima, astrocitima i glija ćelijama, i (3) procenimo njihove efekte na ponašanje i biološke markere u imunološki izazvanim životinjama oba pola podvrgnutim blagom neočekivanom stresu. Procenjujemo da će ciljana isporuka odabranih jedinjenja pomoću nanonosača poboljšati njihove farmakokinetičke (FK) profile, ojačati njihove korisne efekte na raspoloženje, anksioznost i kogniciju i pomoći delineaciji doprinosa neuroimunskih efekata, po svemu sudeći, poreklom uglavnom od mikroglija ćelija. Upoznavanje sa neuroimunskim aspektima i FK optimizacija mogu da podrže napredak u prekliničkom razvoju ovih jedinjenja i obezbede osnov za dizajniranje prospektivnih kliničkih studija.

Literatura

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