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ADVANCED METHODS FOR SELECTIVE INVESTIGATION OF NEURONAL CIRCUITRY: THE FUTURE OF DEVELOPING NOVEL THERAPEUTIC APPROACHES IN NEUROPHARMACOLOGY?

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Recent advances in neuroscience research techniques and methods have allowed researchers to study neuronal activity with unprecedented selectivity and temporal resolution. An important feature of these technical advances is targeting specific neuronal circuits in both healthy and diseased brains. Some of the most advanced methods include opto- and chemogenetics in freely behaving animals. Initially, they were designed as tools to help researchers understand better the mechanisms underlying complex behaviors, but these approaches may usher in a new era of pharmacological discovery in specific fields of neuroscience, such as epilepsy or neuropsychiatric disorders. Chemogenetics is based on a reverse logic compared to a traditional drug discovery process: an engineered drug target is introduced in the relevant brain area using a viral vector, thus enabling highly selective control of neuronal activity using an otherwise inert drug (e.g. clozapine N-oxide) in both loss- and gain-of-function experiments. In this manner, the researchers reduced the seizure activity in epileptic mice and improved cognitive impairments in a mouse model of schizophrenia. However, its application is largely limited to preclinical animal models, and it is still not clear whether chemogenetics can selectively modulate neuronal circuitry and serve as a potential therapeutic option in humans. A relative success of gene therapy has potentially resolved the issue of safely delivering an engineered receptor into the central nervous system, thus increasing its translational value. This presentation aims to summarize recent scientific evidence on the state-of-the-art and provide information on these advances that might stimulate a fruitful discussion during the conference.

SAVREMENE METODE ZA SELEKTIVNO ISPITIVANJE NEURONSKIH KOLA: BUDUĆNOST RAZVOJA NOVIH TERAPIJSKIH PRISTUPA U NEUROFARMAKOLOGIJI?

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Napredak u savremenim tehnikama i metodama u oblasti neuronauka poslednjih godina omogućio je istraživačima da proučavaju neuronsku aktivnost sa visokom selektivnošću i vremenskom rezolucijom. Važna karakteristika ovih tehničkih dostignuća jeste ciljana manipulacija specifičnih neuronskih kola u mozgu zdravih i obolelih jedinki. Jedne od najsavremenijih metoda uključuju opto- i hemogenetiku kod životinja koje nesmetano ispoljavaju svoje ponašanje. Inicijalno, ovi pristupi su bili dizajnirani kao alati koji bi trebalo da pomognu istraživačima da bolje razumeju mehanizme koji leže u osnovi složenog ponašanja, ali oni mogu dovesti do nove ere farmakoloških otkrića u određenim neuronaučnim oblastima, kao što su epilepsija ili neuropsihijatrijska oboljenja. Hemogenetika je zasnovana na obrnutoj logici u poređenju sa tradicionalnim procesom otkrivanja lekova: konstruisani receptor se uvodi u ciljano područje mozga pomoću virusnog vektora, čime se omogućava visoko selektivna kontrola neuronske aktivnosti korišćenjem inače inertnog leka (npr. klozapin N-oksid), kako u eksperimentima sa gubitkom, tako i u onim sa pojačanjem funkcije. Na ovaj način, istraživači su smanjili učestalost epileptičnih napada u miševa i poboljšali kognitivna oštećenja u mišjem modelu shizofrenije. Međutim, primena hemogenetike je u velikoj meri ograničena na pretkliničke životinjske modele i još uvek nije jasno da li može selektivno modulisati neuronska kola i služiti kao potencijalni terapijski pristup kod ljudi. Relativni uspeh genske terapije potencijalno je rešio pitanje bezbednog unošenja konstruisanog receptora u centralni nervni sistem, povećavajući tako translacionu vrednost ovog pristupa. Ovo predavanje ima za cilj da sumira najnovije naučne dokaze i pruži relevantne informacije o navedenim metodama i na taj način podstakne otvorenu diskusiju tokom konferencije.