IN VIVO ADMINISTRATION OF LONG-TERM RELEASE RISPERIDONE MICROPLATES RESTORES TEMPORAL ORDER RECOGNITION MEMORY IN A MURINE MODEL OF SCHIZOPHRENIA

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Background: Schizophrenia is a serious psychiatric disorder characterized by psychotic symptoms, as well as impaired cognitive symptoms. Symptoms tend to fluctuate over time, with periodic relapses and remissions. The standard treatment for schizophrenia consists in the long-term administration of antipsychotics to reduce symptom severity. However, medication adherence is often poor leading to high rates of relapse and hospitalization. Here, we propose a long-term drug delivery system based on PLGA microparticles for the controlled release of risperidone, a second-generation antipsychotic prescribed to schizophrenic patients.

Methods: PLGA micronsized particles were fabricated using a top-down approach to realize square hydrogel microplates (μPLs). μPLs were engineered in terms of geometry and polymer content to modulate the release of risperidone over a prolonged period of time (months). μPLs were characterized for properties relevant to drug delivery, including morphological, physico-chemical, and pharmacological features. Subsequently, μPLs were tested for their *in vivo* efficacy in a murine model of schizophrenia. μPLs were i.p. injected once at the beginning of the study, while free risperidone was injected every day as control. Subsequently, 2, 4, 8, and 12 weeks post injection the temporal order recognition (TOR) test was carried out.

Results: The use of a top-down approach allowed for the precise control of particle geometrical features. Specifically, SEM and volume impedance analysis highlighted a square geometry for μPLs with an average dimension of 20 μm. Risperidone release from μPLs was analyzed via HPLC, and results showed a prolonged release up to 100 days. TOR test carried out 2 weeks after the injection showed a discrimination index (DI) for mice treated with risperidone-loaded μPLs significantly higher than the DI of the untreated ones and comparable to the DI of mice treated with free risperidone. Moreover, the DI of the treated mice was still higher than the one of untreated group even after 4, 8, and 12 weeks, suggesting that the prolonged and constant release of risperidone from μPLs helps restore the temporal order memory impairment.

Conclusions: The precise control of μPL geometry and polymer content allowed us to precisely tailor the kinetics of risperidone release. The therapeutic efficacy of risperidone-μPLs was demonstrated *in vivo* where they helped restore the impaired memory in a murine model of schizophrenia.