Targeted delivery system for therapy of schizophrenia

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The dopamine D2 and the serotonin 5-HT2A receptors play an essential role in neurotransmission. The interaction between those proteins has a key significance since alterations in either serotonin or dopamine neurotransmission have been implicated in many human neurological and psychiatric disorders such as schizophrenia (affects about 1% of human population), anxiety or depression. It’s known that the serotonin 5-HT2A and dopamine D2 receptors can form the complex (heteromers D2-5-HT2A), which is a potential target for novel therapeutics for schizophrenia.

The Clozapine, which is the second generation of antipsychotics (atypical) is more effective than any other one for treating schizophrenia. It has an ability to achieve antipsychotic effect with lower rates of extrapiramidal effects than with older drugs such as haloperidol. Unfortunately atypical drugs addressed only for tiny part of cell population in the brain are non-specifically delivered into all brain areas. Due to side effects of the Clozapine (e.g. agranulocytosis, a condition involving a dangerous decrease in the number of white blood cells, that has led to death in some patients) and its very poor oral bioavailability (<27%) it desirable to develop the method of delivering it only to the site of action, i.e., to apply selectively on heteromers D2-5-HT2A.

One of the “hot” topics of nanomedicine is the incorporation of the therapeutic agents inside biocompatible nanocarriers. The application of nanoparticulate pharmaceutical carriers increases in vivo bioavailability and efficiency of many drugs. Moreover, special surface modification/functionalization of nanocarriers can be used to control their biological properties in a desirable fashion and to enable them to perform therapeutic or diagnostic functions in right place and at right time. The nano-strategy also leads to the lowering of drug dose – reducing unfavorable side effects. Therefore, the aim of our work was to prepare nanocapsules containing Clozapine for targeted delivery to the heteromer D2-5-HT2A. Such goal has been achieved by development of the method of encapsulation of Clozapine into the nanocarriers, which are able to pass through the blood-brain barrier and following synthesis of new antibody specific for dopamine and serotonin D2-5-HT2A heteromer, which will be next used to modify the surface properties of clozapine nanocapsules. In that way we can obtain efficient delivery of the encapsulated clozapine, preferentially to the hetero-dimer site in selected tissues. Development of the new way of selective and controlled clozapine delivery may have a key significance in novel therapy of schizophrenia.

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