Abstract of a series of scientific papers

"The role of trace-amine associated receptors in the manifestation of schizophrenia electrophysiological enophenotypes", submitted for participation in the St. Petersburg State University Prize competition "For Scientific Works", in the category for young scientists.

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The cycle of works (6 articles published from 2018 to 2019) is devoted to the study of the trace-amine associated receptors (TAARs) role in the schizophrenia endophenotypes manifestations in rodent models. Numerous studies confirm that trace amines and their receptors act as neuromodulators, playing an important biological role in the mammalian central nervous system (see reviews by Berry, 2004; Berry et al., 2017; Gainetdinov et al., 2018). TAARs family members, which are relatively well represented in the central nervous system, are TAAR1 and TAAR5 (Gainetdinov et al., 2018). It has been found that violation of trace amine concentration is associated with different psychiatric impairments such as depression, Alzheimer's disease, attention deficit hyperactivity disorder, Parkinson's disease and schizophrenia (Boulton, 1980; Branchek and Blackburn, 2003; Pei et al., 2016; Lindemann and Hoener, 2005; Zucchi et al., 2006; Berry, 2007; Sotnikova et al., 2009).

In the framework of the schizophrenia endophenotypes concept for diagnosing and controlling the development of the disease, it is proposed to use the certain, genetically determined characteristics that are more specific than clinical symptoms (Holzman, 1992, 1996; Gottesman, Gould, 2003; Braff, Light, 2005; Bearden, Freimer, 2006; Turetsky et al., 2007). Active search for a valid and highly specific diagnostic tool, as well as an objective criterion for assessing the effectiveness of psychopharmacotherapeutic interventions, made it possible to consider a number of electrophysiological parameters as neurophysiological schizophrenia endophenotypes, such as sensory gating P50 (SG), mismatch negativity (MMN) and event related component P300 (Turetsky et al. , 2007; Greenwood et al., 2007; Swerdlow et al, 1994; Clementz et al., 1998; Greenwood et al., 2019).

The authors research work is focused on the study of TAAR1 and TAAR5 agonists effect on a complex of the two most promising electrophysiological schizophrenia endophenotypes, such as mismatch negativity (MMN) and sensory gating (SG) (Light, Swerdlow, 2015) in rats and mice. The influence of TAAR1 and TAAR5 agonists on the amplitude-frequency characteristics of rodent event-related potentials was demonstrated. The results obtained indicate that the TAAR1 and TAAR5 agonists have the opposite effect on schizophrenia endophenotypes, which suggests the presence of antagonistic relationships between these two receptors.

It was found that the TAAR1 agonist administration causes a significant increase in the SG index (Aleksandrov et al., 2019d), as well as an increase in the MMN-like response amplitude (Aleksandrov et al., 2019c) in mice. On the other hand, the administration of a TAAR5 agonist has the opposite effect, significantly reducing the SG index in rats (Aleksandrov et al., 2018a), and also leads to a decrease in the amplitude and latency of event related potentials in the SG study paradigm in mice (Aleksandrov et al., 2019b). In the mismatch negativity research paradigm, the TAAR5 agonist administration reduces an MMN-like response. It should be noted that the TAAR5 agonist administration also increases the amplitude of the late positive component of the event-related potential in mice and rats (Aleksandrov et al., 2018b). In addition, a systemic TAAR5 agonist administration was found to cause the specific motor behavior disorders in mice that are similar to the tardive dyskinesia manifestations in humans (Aleksandrov et al., 2018).

Recent studies have shown that TAAR1 and TAAR5 agonists' systemic administration leads to the significant changes in schizophrenia electrophysiological endophenotypes. It is assumed that this may be due to TAARs neuromodulatory effects on classical monoamines systems. An increase in the sensory-gating index (SG) and the mismatch negativity-like response (MMN) in mice after the TAAR1 agonist injection suggests that the TAAR1 activation may help

to normalize the electrophysiological and behavioral disorders that accompany various pathological states, including schizophrenia. On the other hand, a decrease in the pre-pulse inhibition intensity and a decrease in the amplitude and latency of event related potentials in the SG paradigm, as well as an MMN-like response after the TAAR5 agonist injection suggests that TAAR5 may have a potential contribution to the pathophysiology of schizophrenia spectrum disorders.

The presented results are important for understanding the pathophysiology of schizophrenia spectrum disorders. The results confirm the TAARs contribution to the regulation of a number of psychophysiological processes disrupted in schizophrenia. It is assumed that TAAR1 and TAAR5 receptors have an opposite effect on a number of electrophysiological endophenotypes, which can serve for the development of a new antipsychotic drugs generation that will not only compensate the pathophysiology of mental disorder, but also prevent motor impairments arising during the prolonged treatment with existing antipsychotic drugs.