Beneficial effects of xenon on behavior in valproic acid-induced model of autism

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Background

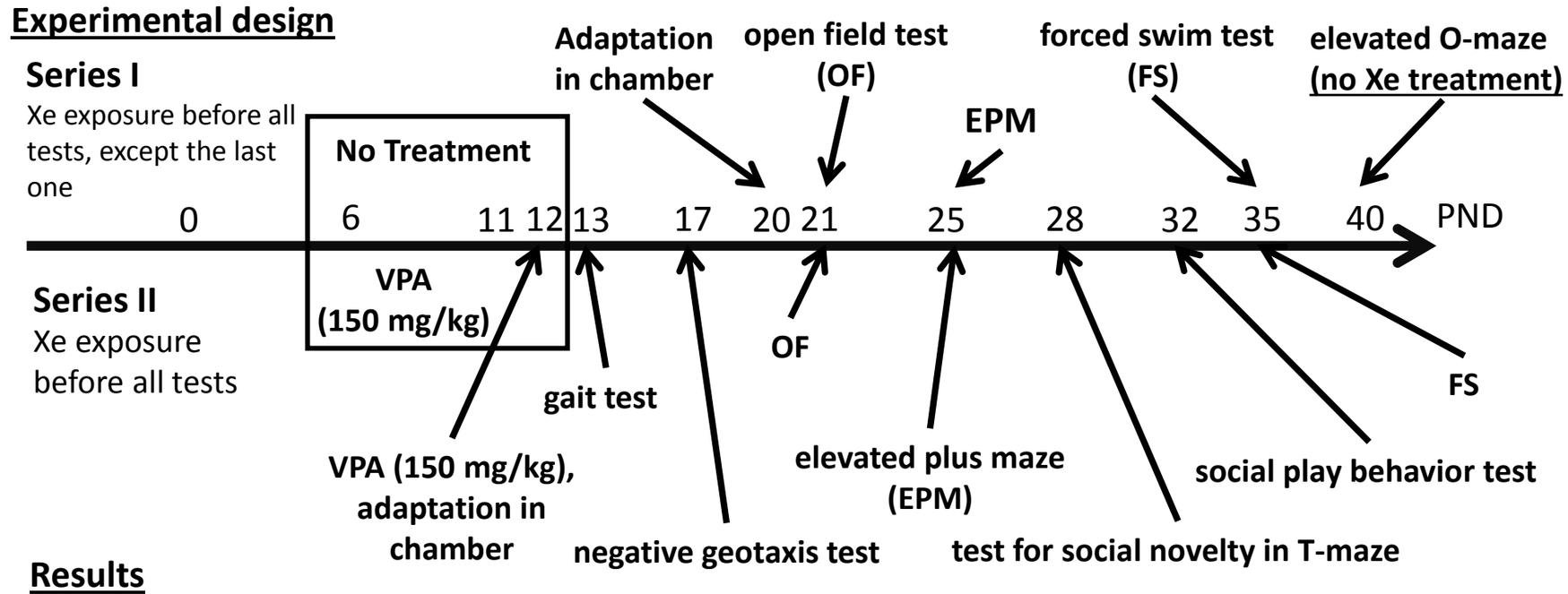
Xenon (Xe) is a noble gas that has been used for the last several decades as an anesthetic gas during surgery. Its antagonistic effect on glutamate subtype of NMDA (N-methyl-D-aspartate) receptors revealed a plausible implication of this gas in treatment of CNS pathologies, including psychoemotional disorders. With regard to ASD, the ability of Xe in the CNS to reduce excitatory neurotransmission (E) and increase in inhibitory neurotransmission (I) suggests it may restore a putative imbalance in E/I present in patients with ASD. To date, there is no literature available on the behavioral effects of Xe administration in rodent models of autism.

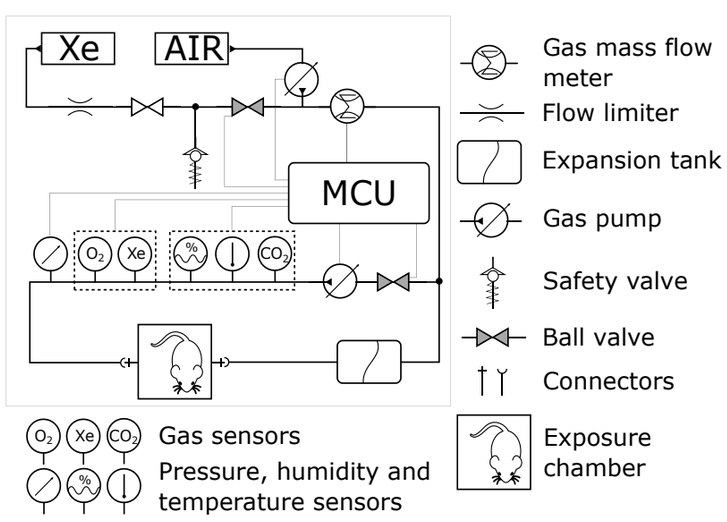
The aim of this study was to assess the behavioral effects of acute inhalation of subanesthetic concentrations of Xe and to study the outcomes of Xe exposure in valproic acid (VPA)-induced rodent model of autism.

Methods

2 series of experiments with a battery of behavioral tests aimed to evaluate locomotion, anxiety- and depression-like behavior, and social behavior in healthy, VPA-treated and Xe-exposed young rats. Xe treatment (10 min, 25%±2.5%) → 10 min in individual cage → 5 min testing. Series I for intact animals included two groups('Control' n=21 'Xe' n= 23), Series II (for the autism model included four groups ('Cont-air' n=13 'Cont-Xe' n=11 'VPA-air' n=14 'VPA-Xe' n=14).

Experimental design

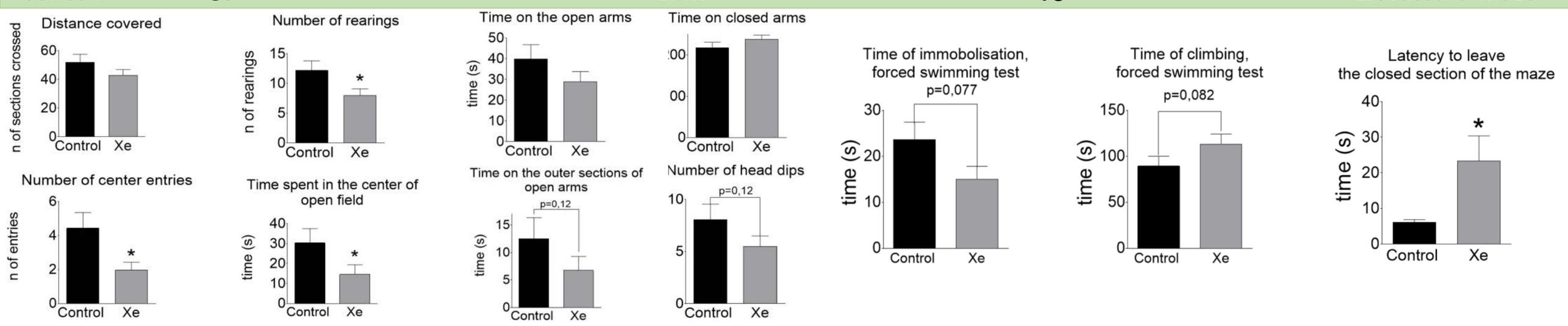




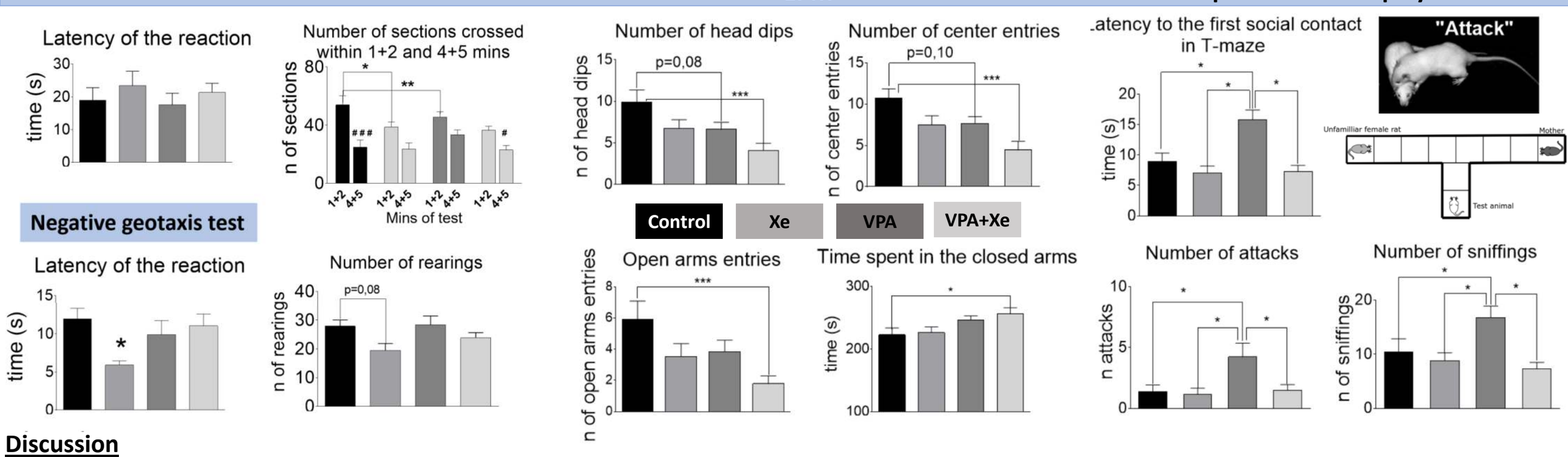
Schematic representation of Xe exposure apparatus.
MCU = micro control unit

Results

Series I



Series II



Discussion

Series I. The exposure to Xe didn't alter either "normal" locomotor activity or "normal" anxiety level of rats in the open field, elevated-plus and elevated O-maze tests. At the same time, Xe administration resulted in reduced exploratory motivation and/or emotionality evoked by novel conditions in OF and OM, and slightly decreased the risk-taking behavior in EPM. In addition, Xe has shown ability to reduce behavioral despair of rats in FS by inducing the switch in the preference towards active escape. The decreased exploratory motivation in OM suggests delayed, long-term effects of Xe inhalation.

Series II. In our study VPA treatment led to increased aggression and anxiety. These effects are the most commonly observed signs of autism in clinical practice. We have not observed any physical or sensorimotor impairment in animals in early infancy, nor locomotor disturbances or depressive-like behavior in adolescence. The most important finding of this study is demonstration of improved social behavior of VPA-exposed rats after a single inhalation of Xe (25%, 10 min). Prominent inhibitory effect of Xe on NMDA receptors makes this gas an attractive modality for studying pathological conditions involving these receptors. Excitation and inhibition imbalances are frequently observed in animal models of ASD and its correction normalizes key autistic-like behavioral patterns. These results suggest that excitation and inhibition imbalances may contribute to the development and maintenance of ASD and represent an important therapeutic target. Rats prenatally exposed to VPA show increased NMDAR levels, enhanced NMDAR-dependent LTP, and hyperconnected local neocortical circuits. In the current work, aggressive behavior as well as social anxiety of rats treated with VPA on PND 6 – 12 at the dose of 150 mg/kg was significantly reduced by acute Xe administration. These data suggest beneficial effect of subanesthetic short-term exposure to Xe and its possible implication in the treatment of psychoemotional disorders such as ASD.

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