Chronic sodium bromide relieves autistic-like deficits in the *Oprm1* mouse model of autism and modulates the activity of serotonin and dopamine receptors *in vitro*

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Introduction:

Autism spectrum disorders (ASD) are complex neurodevelopmental diseases whose diagnosis lies on the detection of impaired social skills together with restricted and repetitive behavior and interests (DSM-5). Although the etiology of ASD remains mostly unknown, impaired excitation/inhibition ratio appears as a common mechanistic feature. Bromide ion is known to reduce hyperexcitability, possibly by competing with chloride ions at channels and transporters and may thus have therapeutic potential in ASD. We evaluated the therapeutic potential of bromide ion in the *Oprm1*^{-/-} mouse model of ASD and the molecular mechanisms involved in bromide treatment, notably effects on GPCRs.

Chronic bromide treatment in *Oprm1* knockout mice: behavioral deficits

Behavioral deficits in *Oprm1*^{-/-} mice:

Impact of chronic bromide treatment in behavioral deficits of *Oprm1*^{-/-} mice, in the two core symptoms of TSA: Social abilities (upper panel) and stereotypes (bottom left panel); and on Anxiety (bottom right panel), a comorbid symptom. Statistics: All: genotypetreatment effect. Except for 3-chamber test: (three-way ANOVA followed by Newman-Keuls post hoc test). 3-chamber test: four-way ANOVA with one repeated measure: stimulus—mouse versus toy followed by Newman-Keuls post hoc test. **P* < 0.05; ***P* < 0.01; ****P* < 0.001 vs. *Oprm1*^{-/-} Saline. Data are presented as mean ± SEM

Bromide dose-dependently restores social interaction and social preference in *Oprm1*^{-/-} mice

Bromide alleviates anxiety in *Oprm1*^{-/-} mice even at low doses.

Chronic bromide treatment relieves behavioral deficits in *Oprm1*^{-/-} mice in a dose-dependent manner

Chronic bromide treatment in *Oprm1* knockout mice: transcriptomics

Bromide impacts the expression of GABA_A subunits involved in E/I balance, *Arc* involved in neuronal plasticity and *Grm2*, *Htr7* (Cpu) and *Grm4* (NAcc) involved in signaling

Bromide and chloride ion effects on 5-HT and dopamine receptor pharmacology

Bromide and chloride behave as Positive Allosteric Modulators on D1R, 5-HT6R and 5-HT7R, but not D2R and 5HT4R

Conclusion:

The beneficial effects of bromide administration in a genetic murine model of ASD and its impact on both gene expression and GPCR pharmacology predicts high translational potential in patients with autism, despite high heterogeneity in etiology and symptoms. The next step will be to test the effects of bromide on mGlu4 and mGlu2 *in vitro*, keeping in mind that Cl⁻ is already known as a good Positive Allosteric Modulator (PAM) of mGlu4, but not such a good one for mGlu2.