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NLX-101 ameliorates responses to hypercapnia in a mouse model of Rett syndrome

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Introduction: Rett syndrome is a neurodevelopmental disorder caused by methyl-CPG-binding protein 2 (MECP2) deficiency. It frequently features ataxic and Cheyne-Stokes breathing. Mouse models of Rett showed reduced hypercapnic ventilatory responses and elevated apnoeic threshold (1) . This phenotype likely contributes to ataxic breathing in other conditions, and hypercapnia improved breathing in a patient with Rett (2). Recently, we demonstrated that NLX-101 (aka F15599), a potent, selective and efficacious agonist with bias for 5-HT_{1A} heteroreceptors (3), improved ataxic breathing in two Rett mouse models. Thus, we investigated the hypothesis that NLX-101 ameliorates impaired hypercapnic ventilatory responses in MECP2 deficient mice.

Methods: We measured minute ventilation (VE) in *Mecp2*$^{tm1.1Coyle}$ heterozygous (R168X) and littermate wild-type (WT) female mice (15±0.3 months-old) using unrestrained whole-body plethysmography. Mice were exposed to increasing fractions of inspired CO_2 ($FICO_2$; 0, 1, 3 and 5%) at 5min intervals. Hypercapnia was performed 20 min after NLX-101 (1.25mg/kg, ip) or vehicle (2.5% DMSO/H_2O, 5mL/kg ip) treatment. Study arm assignment was randomized. Values shown are mean±SEM and were compared using two-factor ANOVA and Tukey's post hoc ($P<0.05$).

Results: Under 5% $FICO_2$, VE was significantly lower in vehicle-treated R168X mice compared to WT (2.52±0.27 vs 3.64±0.16 mL/min/g, $P<0.001$, n=8). Treatment with NLX-101 significantly increased VE in R168X mice (3.46±0.33 mL/min/g, n=8) compared with vehicle-treated R168X ($P<0.01$), rescuing it to WT levels ($P>0.99$). NLX-101 had no effect on VE in WT mice compared to vehicle-treated WT (3.76±0.21 mL/min/g, $P>0.99$, n=8). NLX-101-treated R168X mice showed a trend to increased VE at lower $FICO_2$ but these were not significantly different from vehicle-treated R168X. Under 0% $FICO_2$, NLX-101 significantly reduced apnoea frequency (60±18 vs 295±71 apnoeas/hr, $P<0.01$, n=8) and duration (507±110 vs 911±150 ms, $P<0.01$, n=8) compared to vehicle in R168X. Occurrence of apnoeas in vehicle-treated R168X mice was inversely related to $FICO_2$.

Conclusion: The results demonstrated that NLX-101 rescued hypercapnic ventilatory responses, and reduced apnoea frequency and duration in R168X mice. This positive effect on CO_2 chemosensitivity may be a mechanism by which NLX-101 rescues ataxic breathing in MECP2 deficient mice. The R168X mouse model recapitulates a common mutation occurring in patients with Rett, and has well characterized face validity for translation (4).

References:

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