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Pre-clinical study of NLX-101 for the treatment of apnoeas in two mouse models of Rett syndrome

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Introduction: Rett syndrome (RTT) features profound neurological deficits, and dysautonomia is highly prevalent. This is characterized by apnoeas and irregular respiratory frequency. Previous studies demonstrated that less selective non-biased 5-HT_{1A} agonists reduced apnoeas in mouse models of RTT (1), however 5-HT_{1A} auto-receptor activation has been associated with negative effects on breathing (2). In contrast, NLX-101 is a highly potent, selective and efficacious agonist with functional bias for 5-HT_{1A} hetero-receptors, which are associated with positive effects on respiratory drive (2). Thus, we aimed to investigate the effect of NLX-101 on respiratory dysrhythmias in two RTT mouse models.

Methods: We measured the frequency and duration of apnoeas in $Mecp2^{tm1.1Bird}$ (n=18) and $Mecp2^{tm1.1Coyle}$ (n=22) heterozygous female mice (>6 months old) using unrestrained whole-body plethysmography both acutely and chronically. Acutely, breathing was measured during 1 hour pre-treatment and 1 hour post-treatment with randomly-assigned multiple ascending doses of NLX-101 (0.04, 0.16, 0.63, 2.5 mg/kg, dose volume 1 mL/kg) or vehicle. Chronically, in a separate group of $Mecp2^{tm1.1Coyle}$ (n=22) heterozygous females, a continuous infusion of NLX-101 or vehicle through subcutaneous mini-pumps (7 mg/kg/day) was delivered and respiratory parameters measured before, 7, 10 and 14 days after treatment.

Results: Acute ascending doses of NLX-101 significantly reduced the frequency and length of apnoeas in a dose-dependent manner in both strains. After the highest acute dose of NLX-101 $Mecp2^{tm1.1Bird}$ females presented 12±6 apnoeas/hour compared to 142±12 apnoeas/hour in vehicle treated females (mean ± SEM, ANOVA, $P<0.05$). Additionally, the length of the remaining apnoeas was shorter in the NLX-101 treated group compared to vehicle (0.712±0.712 versus 1.415±0.107 s). The drug was equally effective in $Mecp2^{tm1.1Coyle}$ females, reducing the frequency to 12±4 apnoeas/hour and length 0.862±0.057 s, compared to 153±32 apnoeas/hour and 1.534±0.1 s in vehicle. Chronic continuous infusions reduced the frequency of apnoeas by 65±6, 63±4 and 53±10 % at 4, 10 and 14 days post-treatment, respectively.

Conclusion: The results demonstrated that NLX-101 modified apnoea frequency and duration in a dose-dependent manner in heterozygous females from two mouse strains. The $Mecp2^{tm1.1Coyle}$ model mimics one of the most common mutations (R168X) in patients with RTT, which makes it highly relevant for translation. The present results will guide selection of the dosing schedule of NLX-101 for future clinical trials in patients with RTT.

References:

1. Abdala AP *et al.* (2014). *Am J Respir Cell Mol Biol* **50**: 1031-9.

2. Corcoran AE *et al.* (2014). *J Neurosci* **34**: 51-9.

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