OX1/OX2 receptor antagonist ACT-078573 and the OX2 selective antagonist TCS-OX2-29. Aimed at elucidating SAR requirements in other regions of the molecule and further enhancing OX_1 potency and selectivity, we have designed and synthesized a series of analogs bearing a variety of substituents at the 1-position of the tetrahydroisoquinoline.

Methods: All target compounds were synthesized and characterized by MS, NMR and HPLC. Target compounds were evaluated in calcium-dependent functional assays in RD-HGA16 (Molecular Devices) cell lines stably expressing either the OX1 or OX2 receptor.

Results: The results show that an optimally substituted benzyl group is required for activity at the OX_1 receptor. Several compounds with improved potency and/or selectivity have been identified. When combined with structural modifications that were previously found to improve selectivity, we have identified compounds with apparent dissociation constants (Ke) less than 20 nM at the OX_1 receptor and >500-fold selectivity over the OX_2 receptor. In vivo, select compounds blocked the development of locomotor sensitization to cocaine in rats.

Conclusions: These findings will expedite the development of potent and selective OX1 antagonists as medications for the treatment of OX1-mediated disorders such as drug addiction.

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Effects of environmental enrichment on microRNA-221 expression and ERK phosphorylation in the rat prefrontal cortex following nicotine-induced sensitization or nicotine self-administration

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Aims: The purpose of the current study was to determine the underlying mechanism(s) by which environmental enrichment results in neuroprotective effects in repeated nicotine administration.

Methods: Rats were raised in either an enriched condition (EC) or an impoverished condition (IC) during postnatal days 21–53. Rats underwent nicotine sensitization for 15 days or nicotine self-administration for 21 days. After the final behavioral test sessions, we profiled microRNA (miR) expression using microarrays and examined the phosphorylation levels of ERK1/2 (pERK1/2) in the prefrontal cortex (PFC).

Results: Repeated nicotine (0.35 mg/kg) injections induced pERK1/2 to similar levels in IC rats; however, the induction of pERK1/2 in EC rats by nicotine was not significantly different from saline controls, owing to their high baseline. Similarly, following nicotine self-administration, compared to saline controls, IC rats exhibited increased pERK1 and pERK2, whereas the levels of pERK1/2 were not altered in EC rats. In addition, miR-221 expression was region-selectively upregulated in the PFC of EC rats relative to IC rats after repeated nicotine administration or nicotine self-administration. Overexpression of miR-221 via lentiviral (LV) techniques attenuated nicotine-induced increase in pERK1/2 in PC12 cells. Moreover, LV-miR-221 overexpression in the medial PFC potentiated nicotine-mediated locomotor activity in IC but not in EC rats in response to 15-day repeated nicotine (0.35 mg/kg) injections.

Conclusions: Collectively, these findings suggest that environmental enrichment, via upregulation of prefrontal miR-221 expression, modulates the nicotine-induced ERK activation in the mPFC, which forms a potential mechanism to enhance sensitivity to nicotine

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Psychiatric symptoms among pregnant and newly postpartum women receiving financial incentives for smoking cessation

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Aims: Financial incentives for smoking cessation increase smoking abstinence and decrease Beck Depression Inventory (BDI) ratings among depression-prone pregnant and newly postpartum women. The aim of the present study was to use the Brief Symptom Inventory (BSI) to investigate whether this treatment effect impacts a broader array of psychiatric symptoms than BDI ratings.

Methods: Participants ($N = 289$) were smokers at the start of prenatal care who participated in four controlled clinical trials on the efficacy of financial incentives for smoking cessation. Women were assigned to either an intervention wherein they earned vouchers exchangeable for retail items contingent on abstaining from smoking or a control condition wherein they received vouchers of comparable value independent of smoking status. BSI ratings were examined across 8 antepartum/postpartum assessments. Women who reported a history of prior depression or had BDI scores > 17 at the start of prenatal care were categorized as Depression-Prone (Dep+) while those meeting neither criterion were categorized as Depression-Negative (Dep−). Treatment effects on BSI ratings were analyzed in a three-way repeated measures ANCOVA.

Results: There was a significant three-way interaction of treatment, depression status, and time ($p < .0001$) on BSI Total scores, with the contingent incentives intervention decreasing Total scores below scores in the control condition from late-antepartum through 12-weeks postpartum among Dep+ but not Dep− women. Peak effects occurred at 8-weeks postpartum and included significant reductions across the BSI Depression, Anxiety, Phobic Anxiety, Somatization, Interpersonal Sensitivity, and Psychoticism subscales.

Conclusions: This incentives-based intervention reduces the severity of a broad array of psychiatric symptoms among depression-prone women.

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