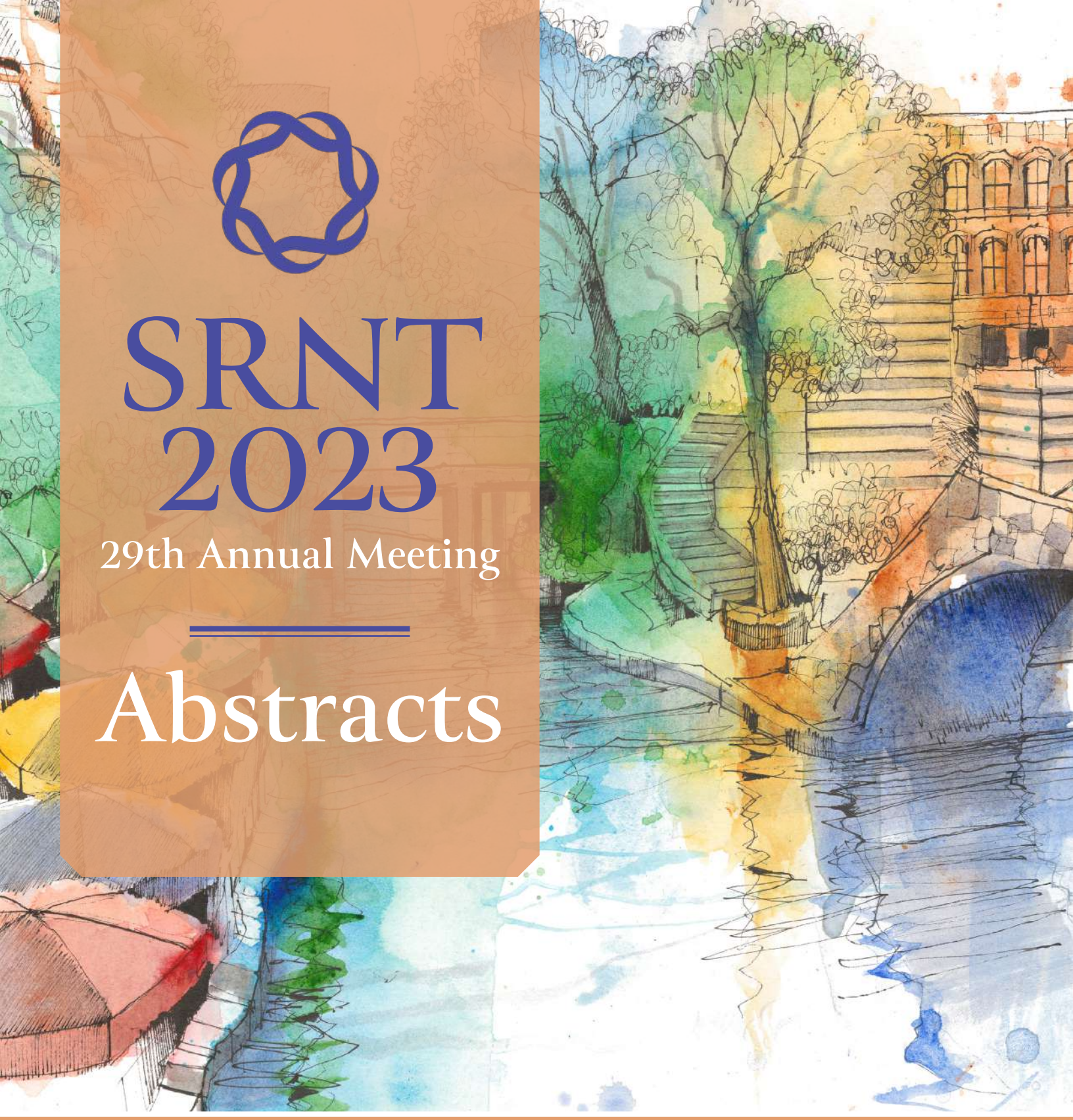

SRNT 2023

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Abstracts

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PAPER SESSION 17: THE DRIVING FACTORS: NEUROBIOLOGICAL MECHANISMS UNDERLYING DRUG USE AND NOVEL THERAPEUTIC APPROACHES

PPS17-1

AVERSION AND PREFERENCE IN MICE TOWARDS NICOTINE ENANTIOMERS IN SYNTHETIC NICOTINE

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Significance: Manufacturers recently introduced synthetic nicotine in e-cigarettes and smokeless products. While tobacco-derived nicotine consists almost exclusively of S-nicotine, the most widely added form of synthetic nicotine is racemic nicotine, consisting of 50% S-nicotine and 50% R-nicotine. Products containing racemic nicotine may have different sensory properties from equivalent products containing tobacco-derived nicotine, modifying initiation and addiction behaviors. Methods: The two-bottle choice assay was used to characterize aversion and preference in male and female C57BL/6 mice to a range of S- and R-nicotine concentrations and racemic nicotine. Mice were presented with choice solutions overnight on 4 consecutive days, given water ad libitum during the day Nicotine enantiomers were validated using gas chromatography / mass spectrometry (GCMS) with a chiral column. Results: On all four days of testing, mice consumed as much from the bottle containing R-nicotine (100 µg/ml, 200 µg/ml) as from the bottle containing plain water. In contrast, S-nicotine was strongly avoided at the same concentrations, with plain water preferred. Racemic synthetic nicotine was preferred over S-nicotine when offered at the same concentrations (100 µg/ml). When racemic synthetic nicotine was offered at twice (200 µg/ml) the concentration of S-nicotine (100 µg/ml), mice consumed equal amounts from both bottles. Conclusions: In mice, the aversive effects of racemic nicotine are determined by its S-nicotine content. R-nicotine did not diminish or strengthen the aversion to S-nicotine. Tobacco products containing racemic nicotine are likely less aversive compared to products containing S-nicotine at identical amounts. Such products might be preferred by beginning users. Since synthetic nicotine products are often labeled inconsistently (for S-nicotine only, or for S- + R-nicotine), consumers may be misled and confused about nicotine content. This study can inform regulatory decisions on tobacco products containing synthetic nicotine, their palatability and product use initiation and addiction.

FUNDING: Federal

PPS17-2

SELF-ADMINISTRATION OF NICOTINE OR COTININE ALTERED PROTEIN LEVELS OF MOLECULAR MARKERS OF THE DOPAMINE SYSTEM AND GLIAL CELLS WITHIN KEY REGIONS OF THE MESOCORTICOLIMBIC PATHWAY

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Background: Nicotine is the primary addictive tobacco component. Cotinine is the major metabolite of nicotine that also shows reinforcing effects in rats. Studies have shown that nicotine alters extracellular dopamine (DA) levels and DA receptor expression within the mesocorticolimbic pathway. Evidence indicates that cotinine can also alter mesolimbic DA levels. However, effects of cotinine on DA receptor levels remain unknown. In addition, glial cells, including microglial cells and astrocytes, are important components of and play important roles in the central nervous system. However, the involvement of glial cells in nicotine and cotinine's effect has been largely unknown. The current study aimed to investigate effects of nicotine and cotinine self-administration on molecular markers of the DA system and glial cells within the mesocorticolimbic pathway. Methods: Adult male Wistar rats were trained to self-administer saline, nicotine, or cotinine under a mixed fixed-ratio (FR) and progressive-ratio (PR) schedule for a total of 5 weeks. Following the last PR session, brains tissue was harvested from key mesocorticolimbic regions including ventral tegmental area (VTA), nucleus accumbens shell (NACsh), nucleus accumbens core (NACcr), prelimbic (PL) and infralimbic (IL) cortices. Total protein was isolated and was subject to Western blotting for determination of astrocytes and microglial cells makers, i.e., glial fibrillary acidic protein (GFAP) and ionized calcium-binding adaptor marker 1(IBA1), respectively, as well as DA markers including tyrosine hydroxylase (TH), D_1 and D_2 receptors (D1R & D2R). Results: Rats readily developed self-administration of nicotine and cotinine. Nicotine and cotinine induced similar infusions during FR schedules, but nicotine induced greater breakpoint than cotinine during the PR schedule. Cotinine self-administration increased GFAP expression in the VTA, and nicotine self-administration increased GFAP expression in the NACcr. Cotinine self-administration also reduced D2R expression in the NACcr. On the other hand, neither nicotine nor cotinine altered IBA1, TH, or D1R expression. Conclusions: These results indicate that nicotine or cotinine self-administration is associated with altered GFAP and/or D2R protein expression within selective mesocorticolimbic regions, suggesting that these molecular alterations may be involved in reinforcing effects of nicotine and cotinine.

FUNDING: Federal

PPS17-3

TARGETING THE D3R-NACHR HETEROMERIC COMPLEX FOR NICOTINE CESSATION

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Tobacco dependence remains one of the largest preventable causes of disease and death worldwide. Unfortunately, currently available therapeutics are only modestly effective in assisting individuals to achieve long-term abstinence. Thus, there is a critical need to identify novel targets for therapeutic intervention. It has been recently shown that nicotinic acetylcholine receptors (nAChRs) and dopamine D3 receptors (D3Rs) form heteromeric complexes on dopaminergic neurons, and a novel compound, HyNDA-1, can enhance the interaction between the nAChR-D3R complex. Thus, in these studies, we sought to examine whether HyNDA-1 modulation of the nAChR-D3R complex could serve as a novel target for therapeutic intervention to promote nicotine cessation. In the first study, mice were examined for the effects of HyNDA-1 on nicotine intake with the intravenous nicotine self-administration protocol. Subjects were tested across a range of HyNDA-1 doses (0-30 mg/kg) in a within-subject Latin-square manner. Based on these findings, we next examined whether HyNDA-1 would alter general operant responding for food reward in a separate cohort . Finally, a third cohort of mice were examined in the conditioned place preference protocol (CPP) to determine if HyNDA-1 infers rewarding or aversive properties at the effective dose for nicotine self-administration. We found that pre-administration of HyNDA-1 attenuated nicotine self-administration in a dose-dependent manner. Interestingly, the effective dose of HyNDA-1 was ineffective in altering food self-administration and did not induce a chamber preference in the CPP test. These data reveal that modulation of the D3R-nAChR complex by HyNDA-1 decreases nicotine self-administration. Importantly, these effects were specific for nicotine, as HyNDA-1 treatment did not alter food self-administration. Moreover, the HyNDA-1 compound does not appear to infer any rewarding or aversive properties by itself, as no differences were found with CPP. Taken together, these findings reveal that modulation of the D3R-nAChR complex has the potential to be an effective novel target for smoking cessation. *Supported by the National Institute on Drug Abuse (NIH DA039658 to CDF) and Tobacco-Related Disease Research Program (TRDRP T30FT0967 to VL).*

FUNDING: Federal; State; Nonprofit grant funding entity

PPS17-4

NICOTINE SELF-ADMINISTRATION IS INVERSELY RELATED TO MEDIAL HABENULAR NEURONAL EXCITABILITY

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Background: Over 23 million people in the United States are dependent on nicotine. However, of the over 70% that wish to quit, only around 7% are successful. One key reason for poor cessation from nicotine is the strong withdrawal and craving that occur after nicotine abstinence. These symptoms have been increasingly attributed to activity in the habenular-interpeduncular nucleus circuit. Our goal is to understand how activity in the medial habenula is altered by changes in nicotine self-administration. Methods: Using C57/B6 adult male and female mice, we employed an e-Vape® self-administration (EVSA) assay using either 6 mg/mL nicotine, 6 mg/mL nicotine + 15 mg/mL menthol, or 60 mg/mL nicotine (with or without menthol). Mice were assigned to fixed ratio 1 (FR1), fixed ratio 3 (FR3), and progressive ratio (PR) responding to measure reinforcement-related and motivation-related behaviors. Following EVSA, brains were extracted for electrophysiology. Neurons in the medial portion of the MHb were identified via a6 nAChR tagged fluorescence and excitability was measured via ex vivo whole-cell patch-clamp electrophysiology. Neuronal excitability was measure through rheobase