Role of Neurokinin Receptors in the Modulation of Nicotine Withdrawal Symptoms and Reward in Mice

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Introduction

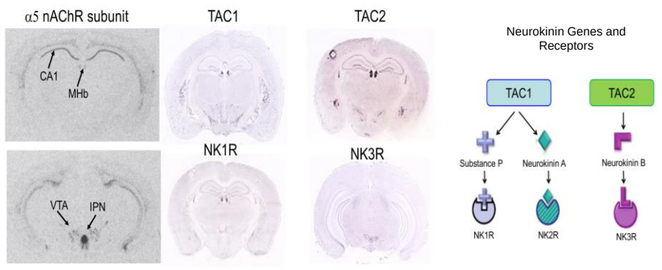
- The use of electronic cigarettes (e-cig) has surged among adolescents.
- Adolescents that experiment with e-cigs are significantly more likely to progress to smoking tobacco cigarettes. [1]
- Regardless of the mode of administration of nicotine (tobacco vs e-cig), there persists a need for effective nicotine cessation aids.
- Current FDA approved treatments are not sufficient to promote cessation in all individuals.

α5-containing nAChRs and Smoking

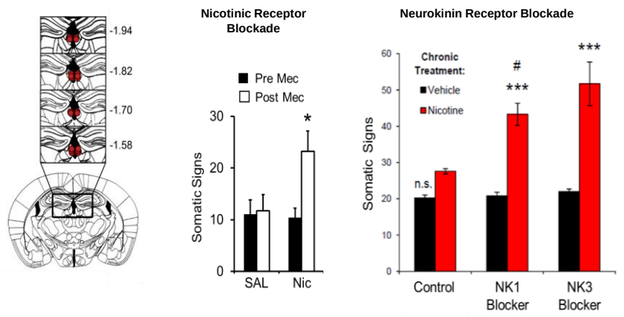
- Genetic studies have highlighted the role of the α5 nAChR subunit in nicotine dependence and lung cancer risk. [2]
- The α5 nAChR subunit has been shown to modulate both the rewarding and aversive properties of nicotine. [3, 4, 5]
- The α5 nAChR subunit expression in the brain is limited, but is found in key brain areas that are known to impact drug abuse. [6]
- ***Problem:*** There are no α5 nAChR selective drugs available.

Neurokinin Receptors as Alternative Targets for Nicotine Cessation

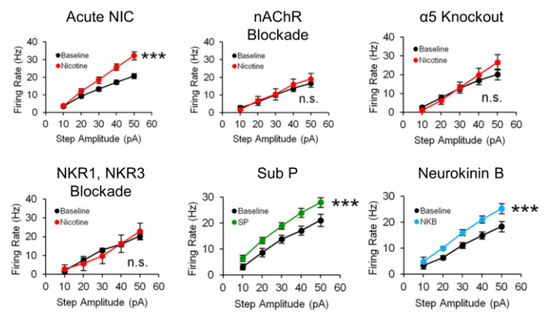
- Neurokinin receptors (NKRs) and transmitters are co-expressed in the same areas as α5 nAChR subunit



- NKRs in the medial habenula (MHb) modulate physical signs of nicotine withdrawal. [6]



- NKRs modulate the firing of MHb neurons in response to nicotine.



Overall Question: Can selective NKR antagonists to be used as viable nicotine cessation aids?

- Aim 1: Determine whether selective antagonism of NKR1 and NKR3 can reduce the rewarding properties of nicotine.
- Aim 2: Determine whether selective antagonism of NKR1 and NKR3 can reduce the reduce the negative affect associated with nicotine withdrawal.

Methods

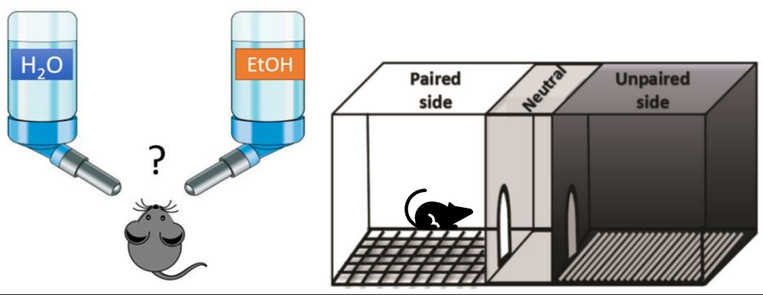
- L-732138 and SB222200, selective antagonists for NK1Rs and NK3Rs respectively, will be used acutely for both aims
- C57BL/6J male and female mice.
- Aim 1: A) Using intermittent two bottle choice measure active oral consumption of nicotine in nicotine dependent animals. B) We will test mice for changes in the development of conditioned place preference.

Nicotine treatment and Consumption Preference:

- 4-6 week old mice are treated with nicotine for mini. Of 6 weeks. (Add 2% saccharine to sweeten solution).
- Afterwards mice will be switched to a two bottle choice paradigm for a minimum of 2 weeks or until stable consumption
- On testing day, mice will receive an injection of the NKR antagonist and nicotine preference and consumption will be measured at 2hr and 24hr

Conditioned Place Preference:

- Nicotine naïve and dependent mice will be given NKR blockers either during the conditioning or testing sessions.



Aim 2: Measure anxiety-like behavior, depression-like behavior, cognitive inflexibility, hyperalgesia and somatic signs during nicotine withdrawal after NKR blockade.

Chronic nicotine treatment:

- 6-8 week old mice are treated with nicotine for mini. Of 6 weeks. (Add 2% saccharine to sweeten solution).

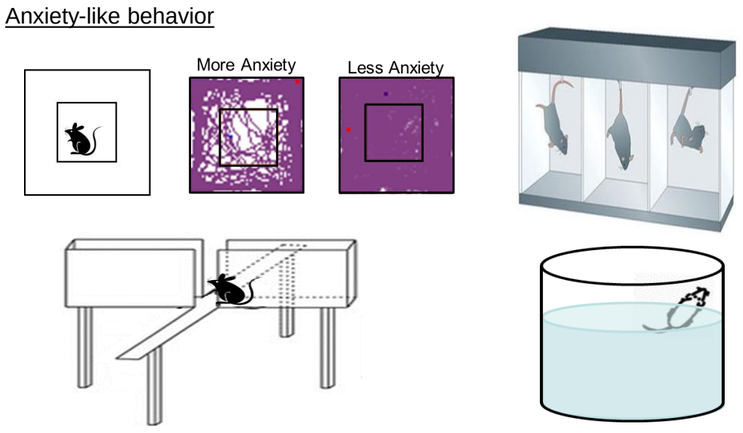
Spontaneous withdrawal:

- Replace treatment water with control water
  - Contains only SAC for 24 hours

Nicotine withdrawal Testing

- Testing Day: Receive an IP injection of the blocker (L-732,138), SB222200 or saline.15 mins later they are placed in the behavioral chamber.
- Behavior Testing: 1 behavior at a time. Mice are placed back on nicotine for a min. Of 48 hours. Next Withdrawal test is conducted

Anxiety-like behavior



Anticipated Result

- We expect to see changes in both rewarding and aversive properties of nicotine use.
  - Aim 1: Blockade of NKR's will reduce nicotine preference and consumption
  - Aim 2: Blockade of NKR's will reduce anxiety- and depression-like behavior.

Future Directions

- Directly infuse NKR blockers into the MHb/IPN axis.
- Measure changes in dopamine release in the nucleus accumbens in response to acute nicotine and NKR blockers in nicotine naïve, satiated, and withdrawn mice.

References

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Acknowledgments

Funded by NIGMS-BUILD grant numbers RL5GM118966, UL1GM118967, and TL4GM118968.