Nicotine addiction is a global health problem that affects nearly one-third of the population. Animal models have shown that the beta-4 subunit of nicotinic acetylcholine receptors (nAChR) expressed in the habenulo-interpeduncular pathway plays a particularly important role in modulating many of the symptoms of nicotine withdrawal in mice. Ibogaine, a naturally occurring compound extracted from the root bark of a West African shrub, has been shown to reduce drug self-administration in animal models of addiction. Ibogaine is considered to be a dirty drug due to its nonspecific interaction at a variety of receptor subtypes. This “nonspecificity” contributes to its hallucinogenic, tremorigenic, and cardiovascular compromising properties. It is thought that the anti-addictive effects of ibogaine are due to its antagonsim of the α4β2 nAChR. In this study we explore the interaction of ibogaine on the α3β4 nAChR with the hope of developing more selective, more effective therapeutics in the treatment of addiction.

Materials/Methods

*Xenopus Laevis* oocytes were injected with mRNA coding for the human α3β4 nicotinic acetylcholine receptor, and incubated for 24-36 hours. Electrophysiological recordings were done using a technique known as two electrode voltage clamp. Compounds were classified according to their IC/EC50 values, the concentrations required to inhibit a response by 50%, or elicit a 50% of maximum response.

Definitions:

Agonist: A compound that elicits a physiological response when it binds to its specific receptor.

Antagonist: A compound that interferes with the physiological action of an agonist.

**Results**

**Introduction**

**Discussion**

EC/IC50 values obtained are in accordance with those found in the literature. Ibogaine and its derivative 18-MC were both found to inhibit 100% of acetylcholine induced ion flux through the α3β4 nAChR. Evidence suggest that antagonism of the α3β4 receptor plays a particularly important role in mediating withdrawal symptoms in the habenulo-interpeduncular pathway. 18-MC retains the same high affinity for this receptor subtype that is required to be an effective therapeutic.

It is currently thought that ibogaine inhibits the α3β4 nAChR in a noncompetitive manner. Preliminary evidence shows that increasing ACh concentrations is able to overcome 18-MC inhibition (Fig 5), suggesting a competitive mode of inhibition. This data is not conclusive however, further experiments must be conducted to determine the voltage dependence of ibogaine binding.

**Future Work:**

- Determine Ibogaine/18-MC binding site
- Explore the voltage dependence of Ibogaine and 18-MC so as to determine channel block.

**Major Findings**

- Ibogaine and 18-MC inhibit 100% of agonist induced ion flux.
- Ibogaine has an IC50 of 2.0±1.1 µM
- 18-MC has an IC50 of 5.8±1.1 µM
- High affinity at the α3β4 nAChR suggests a particularly important role for this receptor in addiction.

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