

Kem, William R.

Department of Pharmacology and Therapeutics
University of Florida College of Medicine

2001 Program
Investigator Initiated (2-year project)

Project Title: Design of a new type of smoking cessation drug

Project Summary: Reducing the incidence of smoking is probably the best means of minimizing the public health problems associated with chronic smoking (or other forms of tobacco self-administration). Currently used smoking cessation therapies that primarily involving nicotine replacement (by transdermal patch or other form of nicotine administration) are not very effective in preventing relapse. One reason may be that the nicotine replacement itself maintains drug dependence. This research team has investigated the potential of various nicotine analogs to serve as alternative smoking cessation drugs. These compounds were synthesized and their pharmacological properties then compared with those of nicotine. Their ability to affect several subtypes of nicotinic receptors was measured using in vitro radioligand binding and electrophysiological methods. Compounds possessing significant receptor binding affinity were then tested for effects on nicotine discrimination and self-administration in whole animals (rats). Finally, the abilities of two of the most promising compounds to enter the brain were measured by microdialysis techniques.

Project Successes: Sites have been identified on the nicotine molecule which can be chemically altered without eliminating binding to nicotinic receptors thought to be involved in smoking addiction. Small molecular substituents on the pyrrolidiny N-group or the adjacent carbon at position 5 may inhibit nicotinic stimulation without eliminating binding to this nicotinic receptor. Even larger substituents added to the 5 position of the pyridyl ring of nicotine were also tolerated, but with some loss of agonist activity. Several of these compounds were shown to be very weak partial agonists. These nicotine analogs were able to readily enter the brain. This project demonstrated that some nicotine analogs possess pharmacological properties desirable in design of new drug candidates for treating tobacco addiction.

Presentations from BRP funded research:

Rowland, N.E., Vaughan, C.H., Bastian, J.R., Robertson, K., Soti, F.S., and **Kem, W.R.** Antagonism of behavioral effects of nicotine in rats by partial agonists. Soc. Neurosci., New Orleans, Nov. 2003 (Abstr. 247.14).

Wildeboer, K.M., LeFrancois, S.E., Papke, R.L., Soti, S.F., and **Kem, W.R.** Nicotine analogs as selective ligands for beta2-containing nACh receptors. Soc. Neurosci., New Orleans, Nov. 2003 (Abstr. 158.6).

Kem, W.R., Prokai, L., Zharikova, A.D., Stevens, Jr., S.M., Cao, X-F., and Soti, F.S. Brain:blood partitioning of DMXBA hydroxy metabolites. Soc. Neurosci., New Orleans, Nov. 2003 (Abstr. 296.23).

New funding based in part on BRP-funded work:

Osprey Pharmaceutical Company, Jacksonville FL
Title: "Nicotinic Drug Design"
Project period: 2004 - 2007

Award amount: \$1,460,000