Summary
Since the composition of n. ChRs is more complex than initially thought, taken together with the observation that all subunits expressed in a subtype contribute to antagonist sensitivity, there may be opportunities to take advantage of this complexity and dynamic responsiveness to set the stage for discovery of subtype-selective n. ChR antagonists, particularly antagonists targeted at the specific n. ChR subtypes important for treating smoking cessation. However, initial studies determined that sazetidine-A did not stimulate 86Rb+ efflux from cells stably expressing _4_2 n. ChRs, suggesting that this compound may not activate n. ChRs [171]. While additional studies are needed, these results are promising and suggest that UCI-30002 may have potential as smoking cessation therapeutic. Development of antagonists selective for n. ChRs mediating nicotine-evoked DA and NE release should retain therapeutic efficacy as smoking cessation agents without producing peripheral side effects.