

**P003** Modulation of nicotinic acetylcholine receptors  
by anabaseine analogues

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Anabaseine analogs (AAs) are partial agonists at the  $\alpha 7$  nicotinic acetylcholine receptor (AChR). This lower efficacy could be caused by at least two possible mechanisms: self-inhibition and/or increased desensitization. To examine the basis for this partial efficacy, we determined the ability of GTS21 and 4OH-GTS21 to inhibit the binding of well-known agonists and antagonists to several AChR subtypes. The results indicate that AAs: (1) bind to AChRs with the following specificity rank order: human (h) $\alpha 4\beta 2$  > h $\alpha 7$  > *Torpedo*. 4OH-GTS21 binds to the *Torpedo* agonist sites with 3.9-fold higher affinity than GTS21; (2) induce desensitization. AAs increase [<sup>3</sup>H]cytisine and [<sup>3</sup>H]TCP binding to *Torpedo* AChRs. Higher concentrations of AAs, however, displace the binding of [<sup>3</sup>H]cytisine (desensitized) and [<sup>3</sup>H]TCP (resting); (3) show higher affinity for the desensitized than for the resting ion channel. GTS21 binds to the TCP locus with 3.7-fold higher affinity than 4OH-GTS21. In the resting state AAs preferably bind to the agonist sites, this contact triggers the desensitization process, and in this state they finally interact with the ion channel. [partially funded by RO1 MH6142 and FBRP BM013 (WK) and by Intramural Grant from the Western University of Health Sciences (HA)].