In Vivo Quantitative Autoradiographic Analysis of Brain Muscarinic Receptor Occupancy by Antimuscarinic Agents for Overactive Bladder Treatment

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Antimuscarinic agents are widely used as the first line therapy for urgency, frequency with or without urge incontinence, all symptoms of the disorder termed overactive bladder (OAB), but chronic administration of antimuscarinic agents in older patients is reported to result in a non-degenerative mild cognitive impairment. Therefore, this study was undertaken to characterize *in vivo* muscarinic receptor binding in the rat brain by quantitative autoradiography. There was a dose-dependent decrease in the *in vivo* specific (+)*N*-[^{11}C]methyl-3-piperidyl benzilate binding in each brain region of rats 10 min after i.v. injection of oxybutynin, propiverine, solifenacin and tolterodine. The rank order of the i.v. dose (RO_{50}) for 50% receptor occupancy of antimuscarinic agents in rat brain regions was propiverine > solifenacin > tolterodine, oxybutynin. The dose ratios of antimuscarinic agents for the brain receptor occupancy (RO_{50}) to the inhibition of carbachol- and volume-induced increase in the intavesical pressure (ID_{50}), which reflects *in vivo* selectivity for the urinary bladder over the brain, were greater for solifenacin, tolterodine and propiverine than oxybutynin. Darifenacin displayed only slight decrease in the (+)*N*-[^{11}C]methyl-3-piperidyl benzilate binding and it was not dose-related. The rank order of the ratio (RO_{50}/ID_{50}) in brain regions to the urinary bladder was solifenacin > tolterodine > propiverine > oxybutynin. Thus, the selectivity for the urinary bladder over the brain was greater for solifenacin, tolterodine and propiverine than oxybutynin. In conclusion, *in vivo* quantitative autoradiographic analysis of brain muscarinic receptor occupancy may provide fundamental basis for managing central nervous system side effects in antimuscarinic therapy for OAB. It is suggested that in the treatment of OAB, central nervous system side effects can be avoided by newer generation of antimuscarinic agents with high selectivity for urinary bladder over brain.