Correction to “Mechanistic Studies of the Allosteric Modulation of Muscarinic Receptors”

In the original version of this thesis, a compiling error omitted two pages (p.69-70) in Chapter 4. These two pages are included below. I apologize for any confusion that resulted from this error.
4.1 Introduction

Allosteric modulation utilizes receptor sites that are physically distinct from the orthosteric site; the orthosteric site is the binding site for the endogenous hormone or neurotransmitter. Targeting these alternate sites provides several potential benefits over the conventional approach of developing orthosterically acting ligands. These benefits may include increased receptor subtype selectivity, decreased toxicity, and the ability to retain spatial and temporal signal patterning (Ellis, 1997; Bridges and Lindsley, 2008). The muscarinic acetylcholine (ACh) receptor family has become a model system for allosteric interactions of class A G protein-coupled receptors (GPCRs), partly because a great deal is known about the location of one of the muscarinic allosteric sites (May et al., 2007). All of the muscarinic receptors are susceptible to allosteric modulation and, for a subset of allosteric ligands, a “common site” has been established. The ligands shown to act at this common site include gallamine, obidoxime, alcuronium, strychnine, and W-84 (Ellis and Seidenberg, 2000; Trankle et al., 2003). Moreover, the high degree of sequence homology in the orthosteric acetylcholine binding site has impeded the development of useful subtype selective orthosteric ligands (Jones et al., 1992). It is believed that targeting regions of the receptor with greater sequence divergence (i.e., allosteric sites) will facilitate the discovery of more subtype selective compounds and allow therapeutic exploitation of the different subtypes (Wess et al., 2007; Langmead et al., 2008b). In agreement with this view, the current set of subtype selective ligands generally act at allosteric sites (Shirey et al., 2008; Bridges et al., 2009; Marlo et al., 2009).
Several models have been proposed to describe how an allosteric ligand can affect a receptor’s binding and response profile (Weiss et al., 1996; Christopoulos and Kenakin, 2002; Ehlert, 2005). The allosteric two-state model (ATSM; Figure 4.1) is a mechanistic representation of allosteric modulation of response (Hall, 2000). It is an extension of the two-state model (TSM; reviewed in Leff, 1995) that incorporates and builds on the ternary complex model (TCM; Stockton et al., 1983; Ehlert, 1988) used to describe multiple receptor binding states attained in the presence of both an allosteric and orthosteric ligand. In the ATSM, the additional receptor states provide the model with the flexibility to address novel forms of ligand-receptor interaction, whereas the cooperativity parameters provide useful means for describing allosteric modulation. The ATSM is formally equivalent to the Cubic Ternary Complex model (CTCM) of Weiss et al. (1996), although, as Hall (2000) has pointed out, the interpretations of some of the parameters differ markedly between the two models. As such, the ATSM reflects both the disadvantages and the advantages of the CTCM; that is, its complexity makes it more suitable for descriptive simulation than for parameter estimation, but it provides a representation of allosteric modulation which is entirely consistent with mechanistic principles of receptor activation. As Weiss et al. (1996) articulated, these models possess “an elegance that can be described in four words: comprehensiveness, symmetry, generalizability, and completeness”.