A molecular model for the bilayer helices of the acetylcholine receptor including an acetylcholine binding site

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A molecular model for the bilayer helices of the acetylcholine receptor is constructed from the 7 channel elements and the 17 hydrophobic helices of the 5 protein subunits. The acetylcholine binding site and the opening to the ion channel are included.

Acetylcholine receptor *Binding site* *Bilayer helix* *Molecular model*

1. INTRODUCTION

We recently presented structural assignments [1,2] for 24 transmembrane segments of the acetylcholine receptor $(AChR)^+$, a membrane complex with 5 subunits, two α- and one each of β-, γ- and δ-subunits [3,4]. Derived from the complete amino acid sequences for the subunits [5–10], 17 of these segments had marked hydrophobic character, and the other 7 segments were identified as channel elements on the basis of single group rotation (SGR) theory [11]. We have also shown that the channel elements can constitute an acetylcholine binding site [12], and we now present a molecular model for all of the helices of the AChR in the bilayer. The order of the subunits, α-, β-, α-, γ- and δ-, around a central 'pit' [13,14] is now favored [15,16].

2. THEORY AND DISCUSSION

The channel elements chosen on the basis of single group rotation theory included both hydrophilic channel-active amino acid side chains and hydrophobic side chains. We have noted that this combination might be necessary for the compatibility of the channel with the bilayer. The 17 hydrophobic helices can be fitted to the 7 ion channel helices by approximating non-polar and polar groups. The result for the first level is shown in fig.1. Selected helices, represented in a simple way (see caption, fig.1), are labeled as they appear in the sequence of a particular subunit. The α-helices are brought together in a way which maximizes electrostatic interactions on one side and hydrophobic 'bonding' to hydrophobic helices and/or phospholipids on the other.

The channel elements were chosen [1,2] on the basis of a model which proposed that a channel amino acid sequence might be glu(1), lys(5), glu(8) or lys(12). In fact, a high proportion of the charged amino acids at the SGR-designated locations in channel elements of all 5 AChR subunits are lys (21/21) and glu (16/28) [1,8]. Channel elements from the β-, γ- and δ-subunits were combined with the 'nucleus' afforded by the ACh binding site by matching those groups which would maximize the electrostatic interactions. The overall result of adding the hydrophobic helices to the ion channel is, for the most part, harmonious and supports the idea that our model for the bilayer portion of the acetylcholine receptor is reasonable.

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Abbreviations: AChR, acetylcholine receptor; ACh, acetylcholine; glu, glutamate; asp, aspartate; lys, lysine; SGR theory, single group rotation theory

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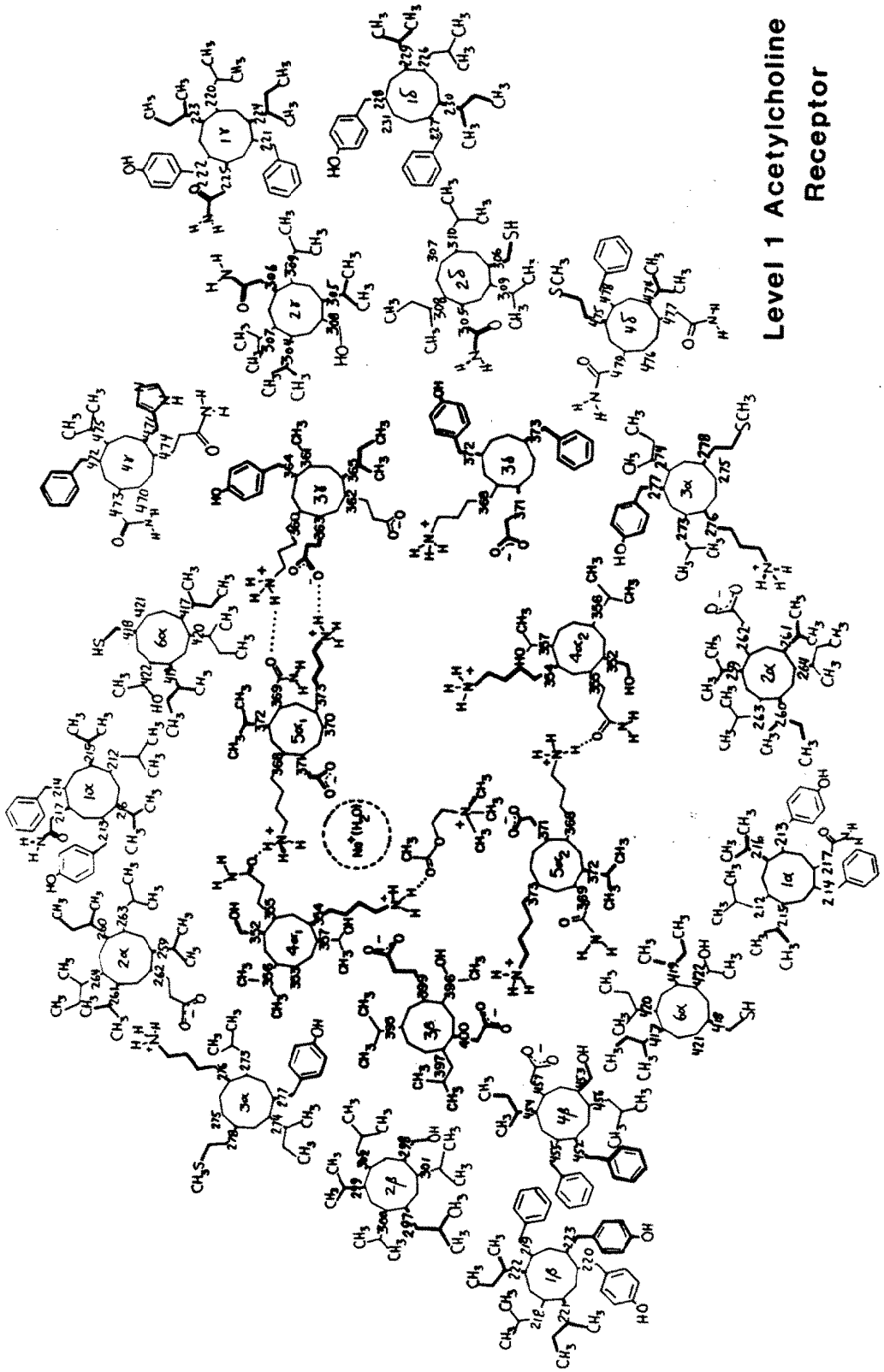

Fig.1. First level of the bilayer portion of the acetylcholine receptor, including the hydrophobic helices, the ion channel and the binding site with acetylcholine in the open conformation. The channel elements (transmembrane helices of 24 amino acids, about 7.3 turns) are divided into 4 levels of 6 amino acids each. Each level is represented as a nonagon; the vertices numbered 1, 4, 7, 9, 3 and 6 are designated as the sites for the amino acids, a span corresponding to 1.52 turns of an α-helix. Continuing the vertex numbering through a second level nonagon with 8, 2, 5, 7, 1 and 4, we note that the 11th amino acid is correctly found in the same orientation as the first, but 3 turns down. Although this representation for the α-helix is approximate, it is simpler and faster to use than a 'helical wheel' [19–21]. Light lines to side chains are used for the first 3 amino acids ('first' turn), dark lines for side chains for the next 3 amino acids ('second' turn). Proximal groups in adjacent helices are thus identifiable.

The model is consistent with the structural information reported for the AChR.

(i) The division of material between exocellular (>50%), bilayer (<36%) and endocellular (<13%) regions [16]. On the basis of the model, the distribution of material among these regions is 59.8%, 24.7% and 15.5%, respectively;

(ii) The relative orientations (50–80°) of the β- and δ-subunits as revealed by electron microscopic examination of a specially prepared AChR trimer [3,17]. The 4β-Na^+-4δ-angle derived from the molecular model in fig.1 is 80–90°;

(iii) The 25% α-helix determined by Raman spectroscopy [18]. The model includes 24 α-helices with 576 amino acids out of the 2333 amino acids in the receptor; i.e., 24.7% α-helix.

The details of construction of the AChR ion channel and other molecular aspects of the AChR will be described in subsequent communications (E.M. Kosower, in preparation).

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