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A Review: The Role of Functional Groups in the Binding of Acetylcholine and Nicotine to Muscle-type nAChRs

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Abstract. This essay discusses the different affinities of acetylcholine and nicotine for muscle-type acetylcholine receptors (nAChRs) due to their different chemical structures and binding mechanisms. Muscle-type nAChRs are pentameric receptors composed of five protein subunits, with the alpha subunit directly interacting with acetylcholine or nicotine. Acetylcholine binds to muscle-type nAChRs through key functional groups, including the carbonyl group and the quaternary ammonium cation, and specific interactions with tyrosine, serine, and tryptophan residues. Nicotine binds to muscle-type nAChRs through weaker interactions with the pyridine and pyrrolidine rings, as well as with polar or charged residues in the binding site. The strengths of the hydrogen bonds and pi-cation interactions involved in acetylcholine and nicotine binding are relatively weak.

Keywords: Acetylcholine; nicotine; muscle-type nAChRs; binding mechanism; functional groups; amino acid residues; hydrogen bonds; pi-cation interactions; affinity.

1. Introduction

Muscle-type acetylcholine receptors (nAChRs) are one types of nAChRs that present on the neuromuscular junction, opening the ion channel to allow transmission of neuro signals when acetylcholine or nicotine bind to them. Acetylcholine and nicotine binds to the same orthosteric binding site on the two alpha subunits (α1 and α2) of muscle-type acetylcholine receptors (nAChRs). Thus, acetylcholine and nicotine compete to bind when they present on the same neuromuscular junction. Acetylcholine has a higher affinity than nicotine for muscle-type nAChRs, because these two molecules have different chemical structures that allow them to interact with nAChRs in different ways. This means that nicotine can activate these receptors, but it requires much higher concentrations of nicotine than are typically achieved through smoking or other forms of nicotine use [1].

The mechanism underlying this difference in affinity has been studied extensively and is thought to be due to several factors, including the key factor of the different binding mechanism contributed by the different chemical properties of the functional groups contained in nicotine and acetylcholine [2].

In this essay, the chemical structure and properties of acetylcholine, nicotine, and muscle-type nAChRs, as well as the mechanism of interaction among them, will be discussed to explain this phenomenon.

2. Muscle-type nAChRs

2.1 General Features

Muscle-type nAChRs are a type of ionotropic receptor that are primarily found at the neuromuscular junction, where they mediate the transmission of signals from the nervous system to skeletal muscle fibers. Muscle-type nAChRs are pentameric receptors composed of five individual protein subunits, arranged in a circular pattern around a central ion channel. The subunits are alpha (consist of alpha1 (α1) and alpha 2 (α2)), beta (β), delta(δ), and gamma (γ) or epsilon (ε) (gamma subunit present in fetal nAChRs, while epsilon subunit present in adult nAChRs), arranged in a 2:1:1:1 stoichiometry respectively. The alpha subunits are the only subunits in muscle-type nAChR that directedly interact with acetylcholine or nicotine [3].

2.1.1 Alpha Subunits

The alpha subunits are encoded by multiple genes, which are categorized as the alpha1 subunit. Both alpha1 and alpha2 subunit are the primary contributor to the acetylcholine binding site in muscle-type nAChRs. During embryonic development, muscle nAChRs may contain a combination of alpha1 and alpha2 subunits. As muscle development progresses and reaches the adult stage, the alpha1 subunit becomes the predominant isoform in most muscle nAChRs [4]. Since the intake of nicotine seldom occur during the embryonic development, this essay mainly focuses on the binding mechanism of alpha1 subunit.

The alpha subunit1 is a transmembrane protein that contains a large extracellular domain, a single transmembrane helix, and a short cytoplasmic domain. The binding to acetylcholine or nicotine is mainly responsible by the extracellular domain. It contains a large number of amino acid residues, including tyrosine, tryptophan, and serine, which form the binding side and are thought to interact directly with the acetylcholine or nicotine molecule [5].

2.1.2 Other Subunits

Beta, delta, gamma and epsilon subunits of the nAChRs do not directly interact with acetylcholine. They are involved in stabilizing the overall structure of the receptor and helping to form the ion channel that allows the influx of cations into the muscle fiber upon acetylcholine binding. These subunits have few effects on the mechanism of acetylcholine or nicotine binding with the nAChRs [6].

3. Acetylcholine

3.1 General Features

Acetylcholine is a neurotransmitter that is widely distributed throughout the nervous system and is involved in a variety of physiological processes, including muscle contraction [7].

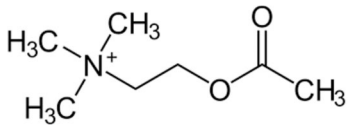


Fig. 1 Chemical Structure of Acetylcholine

3.2 Functional Groups

Chemically, acetylcholine has a condensed formula of (CH3)3N+CH2CH2OCOCH3, which is composed of acetyl group and choline group. Precisely, the acetyl group has a carbonyl group (-CO), which is a polar functional group since there is a partial positive charge on the carbon atom and a partial negative charge on the oxygen atom. The choline group contains a quaternary ammonium cation, N+(CH3)3, which has a positive charge due to the presence of the nitrogen atom; additionally, a hydroxyl (-OH) group is also contained in the choline group, which is a polar functional group that can form hydrogen bonds with other molecules or functional groups [7].

Besides, hydroxyl group (-OH) and ether group (-O-) are also presented in acetylcholine, however, they are considered to play less significant role in the binding mechanism but contribute to the overall structure of acetylcholine [6].

3.3 Binding Mechanism

Acetylcholine binds to the muscle-type nAChR through a variety of chemical interactions with multiple amino acid residues in the receptor complex. The key functional groups, the carbonyl group and the quaternary ammonium cation, and residues, tyrosine, serine, and tryptophan, are involved in acetylcholine binding to muscle-type nAChRs.

3.4 Interactions

3.4.1 Carbonyl Group

The carbonyl group of acetylcholine interacts with the tyrosine and serine residues in the alpha subunit of the nAChR complex through hydrogen bonding interactions. The hydroxyl (-OH) groups in these residues can form hydrogen bonds with the carbonyl oxygen atom, stabilizing the interaction between acetylcholine and the receptor [6].

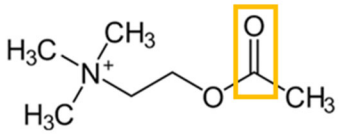


Fig. 2 Carbonyl Group in Acetylcholine (in yellow square)

3.4.2 Nitrogen Atom

The nitrogen atom of the quaternary ammonium cation of acetylcholine interacts with the tryptophan residue in the alpha subunit of the nAChR complex through a pi-cation interaction. The indole ring in tryptophan consists of a benzene ring fused to a five-membered pyrrole ring, creating a delocalized pi-electron system to attract the nitrogen cation [8].

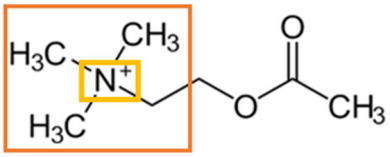
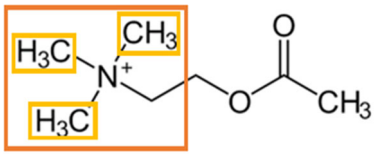


Fig. 3 Nitrogen Atom (in yellow square) in Quaternary Ammonium Cation (in red square)

3.4.3 Methyl Groups

The methyl groups of the quaternary ammonium cation of acetylcholine are located near the nitrogen atom and can also contribute to the pi-cation interaction with the tryptophan residue in the alpha subunit of the nAChR complex [8].



Fug. 4 Methyl Groups (in yellow square) in Quaternary Ammonium Cation (in red square)

4. Nicotine

4.1 General Features

Nicotine is a naturally occurring alkaloid that is found in the tobacco plant (Nicotiana tabacum) and in some other plants in the nightshade family. It is a highly addictive psychoactive drug that acts on the nervous system by binding to nicotinic acetylcholine receptors [9].

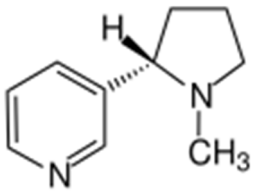


Fig. 5 Chemical Structure of Nicotine

4.2 Functional Groups

Nicotine has a formula of C10H14N2, and it has three key functional groups: the pyridine ring, an electron-rich six-membered aromatic ring with one nitrogen atom, which has the formula -C5H5N; the pyrrolidine ring, a five-membered non-aromatic ring with one nitrogen atom, which has formula (CH2)4NH.; the secondary amine group, a functional group contained in the pyrrolidine ring, which has the formula NH(CH2)3 [9].

4.3 Binding Mechanism

Nicotine binds to muscle-type nicotinic acetylcholine receptors (nAChRs) through a series of specific interactions between its functional groups and the amino acid residues within the receptor's binding site. The mechanism of binding involves the following key functional groups in nicotine and their corresponding interactions with the receptor.

4.4 Interactions

4.4.1 Pyridine Ring

The pyridine ring in nicotine is an electron-rich aromatic ring that interacts with the electron-poor aromatic residues, such as tryptophan and tyrosine, in the binding site of the alpha subunit of the nAChR through pi-stacking interactions. These interactions are relatively weak, but they help to orient the nicotine molecule within the binding site and contribute to the overall binding affinity of the receptor [10].

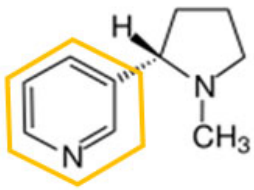


Fig. 6 Pyridine Ring (in yellow hexagon)

4.4.2 Pyrrolidine Ring

The pyrrolidine ring in nicotine contains a secondary amine group that is able to form hydrogen bonds with polar or charged amino acid residues, such as aspartate or glutamate, within the binding site of the alpha subunit. These interactions help to orient the nicotine molecule within the binding site and contribute to the overall binding affinity of the receptor. Additionally, the pyrrolidine ring is relatively hydrophobic, which allows it to interact with nonpolar residues in the binding site, such as leucine and isoleucine [10].

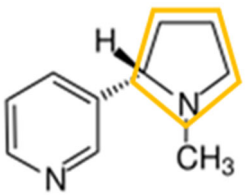


Fig. 7 Pyrrolidine Ring (in yellow pentagon)

4.4.3 Secondary Amine Group

The secondary amine group in nicotine is able to form hydrogen bonds with polar or charged amino acid residues, such as aspartate or glutamate, within the binding site of the alpha subunit. These interactions help to orient the nicotine molecule within the binding site and contribute to the overall binding affinity of the receptor. Additionally, the secondary amine group can be protonated, which makes nicotine a basic molecule and helps it to interact with the acidic residues in the binding site [10].

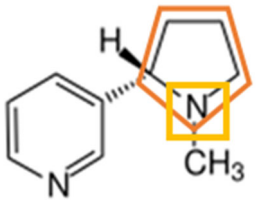


Fig. 8 Secondary Amine Group (in yellow square) in Pyrrolidine Ring (in red pentagon)

5. Bond Energies

The strength of the hydrogen bonds formed between the carbonyl group of acetylcholine and the tyrosine and serine residues in the alpha subunit of muscle-type nAChRs is around 1-5 kcal/mol [11]. The pi-cation interaction between the nitrogen atom of the quaternary ammonium cation of acetylcholine and the tryptophan residue in the alpha subunit of muscle-type nAChRs has an estimated strength of around 2-5 kcal/mol [12].

The strength of the hydrogen bonds formed between the secondary amine group in nicotine and the polar or charged residues in the binding site of muscle-type nAChRs is also relatively weak, with estimated strengths of around 1-3 kcal/mol [11]. The pi-stacking interactions between the pyridine ring of nicotine and the aromatic residues in the binding site of muscle-type nAChRs are also relatively weak, with estimated strengths of around 1-3 kcal/mol [12].

6. Evaluation

The mechanism of binding for both acetylcholine and nicotine involves specific interactions with the amino acid residues within the receptor's binding site. However, acetylcholine has a more extensive and stronger interaction network with the receptor, involving several key functional groups and residues, including the carbonyl group, the quaternary ammonium cation, and tyrosine, serine, and tryptophan residues. In contrast, the mechanism of binding for nicotine involves weaker interactions, particularly with the pyridine ring and pyrrolidine ring, which interact with tryptophan, tyrosine, and polar or charged amino acid residues in the binding site.

7. Conclusion

The differences in the chemical structures and binding mechanisms of acetylcholine and nicotine contribute to their different affinities for muscle-type nAChRs. Acetylcholine has a higher affinity for the receptor due to its ability to form stronger and more extensive interactions with key functional groups and amino acid residues in the receptor's binding site. Nicotine can also activate these receptors, but it requires much higher concentrations. However, as a complex system, there are various mechanisms underlying unclear, which is still a challenging task for the researchers. Understanding the mechanism of interaction between these molecules and the nAChRs can provide insight into the development of new treatments for diseases that affect these receptors.

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