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Acetylcholine: What happens when it interacts with reducing agents?

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Summary. Animal organisms produce acetylcholine that is the main neurotransmitter in the parasympathetic nervous system, as well as neurotransmitter performing neuromuscular transmission. This paper presents possible mechanism for acetylcholine in vivo transformation into free radical state in the reaction with reducing agents and its action by a free radical chain reaction mechanism.

Keywords: acetylcholine, free radicals, reductases, NADH, NADPH.

Acetylcholine is the main neurotransmitter in the parasympathetic nervous system, as well as neurotransmitter performing neuromuscular transmission. Acetylcholine is contained in vesicles of the presynaptic nerve endings, which upon excitation it is released from these vesicles into the synaptic cleft, thereby affecting neurotransmission [8, 12, 17].

Acetylcholine is also synthesized in epithelial and immune cells [7, 13], in plant cells, lichens, fungi and bacteria [6, 10, 16, 20], it was also found in snake venoms [19].

Herein, I do not consider the published data on the mechanisms of acetylcholine action at the molecular level [see review 11, 14], and I propose a possible alternative mechanism of acetylcholine action.

The chemical properties of acetylcholine come from its molecular structure: it is a quaternary ammonium compound which contains a quaternary nitrogen atom, deprived of an electron. Also, according to the chemical structure, acetylcholine is an ester of choline and acetic acid.

Quaternary ammonium compounds are stable in acidic medium and are decomposed in alkaline medium [15]. By this one can explain the acidic environment in the synaptic vesicles (pH~5.5) [1, 21], because in an alkaline medium acetylcholine cannot long exist as an integral structure and can degrade. However, well known the decomposition reaction of quaternary ammonium salts in the Hofmann elimination reaction (also known as exhaustive methylation) in an alkaline medium can occur at elevated temperatures [15]. This is a major obstacle to rapid and complete disintegration of quaternary ammonium compounds *in vivo* including acetylcholine (pH~7.4 in the synaptic cleft). This was confirmed in our experiments, when acetylcholine was placed in solutions pH 7.3-9.8, ethylene in amounts sufficient for analysis in a gas chromatograph was not detected. Small amounts of ethylene were found in experiments when to the acetylcholine powder in vials was added a drop of the alkaline solution or 0,9% NaCl [9].

Acetylcholine may interact *in vivo* with both free radicals and antioxidants within the cells. It is recognized that the postsynaptic membrane is the starting point for the acetylcholine action [8, 17].

Redox reactions constantly occur in the plasma membrane. In redox reactions (also known as oxidation-reduction reactions) one or more che-

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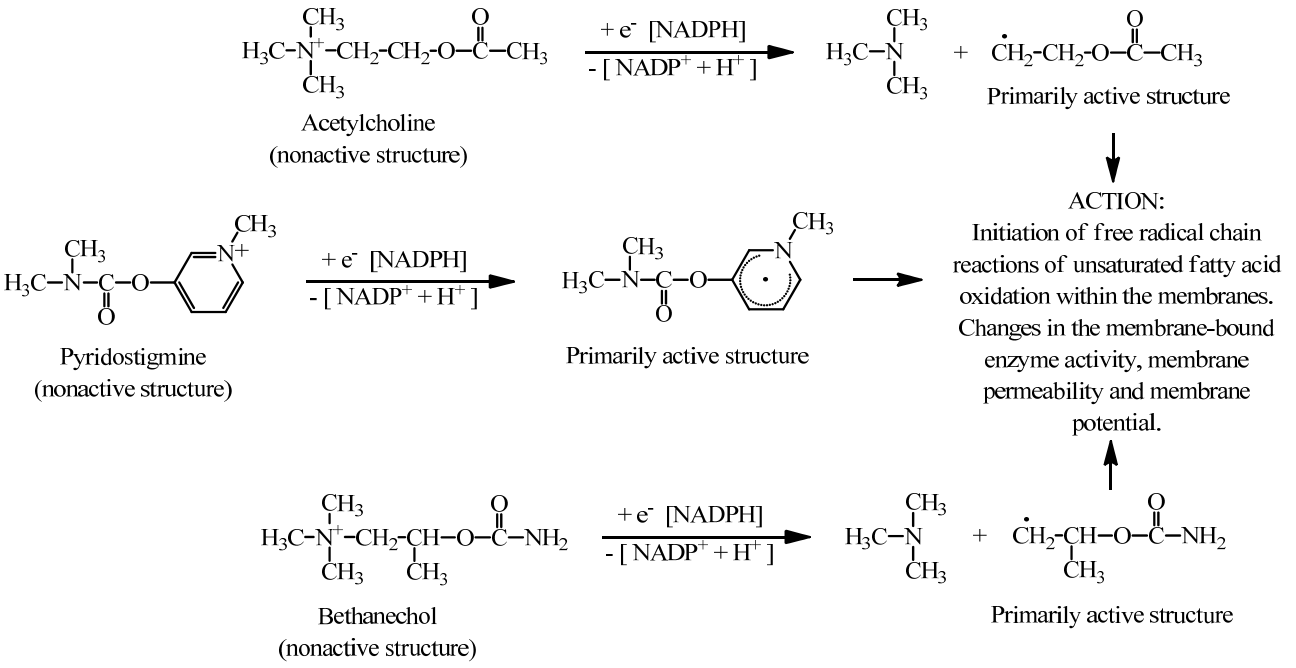

Figure 1. Possible mechanisms of activation and mode of action for acetylcholine, pyridostigmine and bethanechol. Reducing agents in the membranes can be presented by NADPH and NADH.

micals are oxidized (a process in which a molecule loses an electron) while one or more chemicals are reduced (a process in which a molecule gains an electron).

Of particular interest are reducing agents. Among the reducing agents on the cell membranes are reducing enzymes NADH-cytochrome P450 reductase and NADPH-cytochrome P450 reductase [2-5, 18].

Taking into account all the about-mentioned research data, possible mechanisms of activation and mode of action for acetylcholine, pyridostigmine and bethanechol are shown in Figure 1. In the reaction with reducing agents at the postsynaptic membrane acetylcholine decomposes to form a neutral molecule and free radical trimethylamine acetate. Simultaneously acetylcholine in the synaptic cleft is also destroyed in non-enzymatic reaction to form choline and acetic acid.

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Ацетилхолін: що відбувається при його взаємодії з відновлюючими агентами?

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Резюме. Тваринні організми продукують ацетилхолін, який є основним нейромедіатором парасимпатичної нервової системи, а також нейромедіатором між нервами і м'язами. У статті описано можливий механізм трансформації ацетилхоліну *in vivo* у вільнорадикальний стан у реакції з відновлюючими агентами та його дії по механізму ланцюгових вільнорадикальних реакцій.

Ключові слова: ацетилхолін, вільні радикали, відновлювачі, NADH, NADPH.

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