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Mini-review: Molecular Targets of Neuromuscular Blocking Agents on Nicotinic Acetylcholine (ACh) Receptor

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Abstract

Neuromuscular blocking agents (NMBAs) are the drugs that most frequently involved in IgE-mediated anaphylaxis during anesthesia which can lead to perioperative morbidity and mortality. The nicotinic acetylcholine receptor is an ion channel composed of ligands consisting of 5 protein subunits. Receptors Nicotinic acetylcholine is extensively expressed to include both receptors of heteromeric or homomeric combinations of α2–α10 and β2–β4 subunits and medicines that act as nicotinic acetylcholine receptor blockers. The mesolimbic pathway in the ventral tegmental area (VTA) and nucleus accumbens mediates neuronal excitability and dopamine (DA) neurotransmission through the use of ethanol and nicotinic acid (NAc). Drugs belonging to the nicotinic acetylcholine categories are Sugammadex, Gantacurium, Cyclodextrin, Vecuronium, Pancuronium, Rocuronium, and Edrophonium. Enzyme Cholinesterase is an enzyme that degrades Ach released through the neuromuscular synaptic cleft.

Keywords: *NMBAs, nicotinic acetylcholine, cholinesterase, neuromuscular.*

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INTRODUCTION

Receptors Ligand-gated ion channels is glycoprotein that crosses membrane cell and complex assembled protein groups to form porous or canal. Ligand-activated ion channels will respond to specific ligand molecules that exist in the extracellular area where the ion channel is. Conformation and interaction through a binding specific position called a receptor ion channel. Examples are receptor acetylcholine nicotinic, GABAA receptor, AMPA receptor, receptor NMDA glutamate, and serotonin 5-HT3 receptor as well. (Ikawati Z, 2018).

This mini-review will discuss one of ligand-activated ion channel receptor. Acetylcholine nicotinic (nAChR) is the focus to be discussed in further. Dale, Loewi, and Feldberg are the scientist that bring of and reported that Acetylcholine is a neurotransmitter in around early of 20th century. Acetylcholine will react to the nerve center or nerve peripheral autonomic system and the main neurotransmitter in the ganglion. Receptors acetylcholine nicotinic (nAChR) is a composed protein of the five subunits namely a2 which can play a role or be involved in the formation of ion channels with two possible bonds with the molecule acetylcholine. Receptors of acetylcholine nicotinic located at the neuromuscular junction, adrenal medulla, autonomic ganglia, and arrangement nerve center. (Ikawati Z, 2018).

Receptors acetylcholine nicotinic (nAChR) related to the mechanism of go out an influx of Na+ ions crossing the membrane. nAChR is well arranged in such a shape so that pore central can change its permeability to ions. It is also depending on whether the receptor interacts with an agonist or not. nAChRis embedded in a lipid bilayer and thicker from the membrane. This designed the conformation stand out to room intracellular and extracellular. Since its ability to contain several combinations of different subunits, this formed several subpopulations of nAChR. (Alexandris et al., 2021).

Receptor of acetylcholine nicotinate nerves involved as general molecular targets for nicotine and ethanol in recent several years and has been a viable target for the development of novel medications for alcohol addictive. This receptor which widely expressed is pentameric ligand-gated, can be heteromeric or homomeric in different combinations with the α2–α10 and β2–β4 subunits. The binding of acetylcholine (ACh, an endogenous ligand) or nicotine (exogenous ligand) induces a conformational change in the channel, allowing entry of cations.In contrast, ethanol is not a direct agonist on nAChRs but can potentiate the response of these receptors to ACh (Alexandris et al., 2021).

Through direct or indirect modulation of nAChRs located in ventral tegmental area (VTA) and nucleus accumbens (NAc), ethanol and nicotine mediate neuronal excitability and dopamine (DA) neurotransmission in the mesolimbic pathway, and receptors contribute significantly to the effects strengthening of the drug. In the NAc, limited arrays of nAChR subtypes [α4β2, α6β2(β3), α4α6β2(β3) and α4α5β2] have been identified at presynaptic dopaminergic terminals that are important mediators of neurotransmitter release in this region. In contrast, the VTA expresses a more diverse subtype of nAChRs that localize extra-synaptically at dopaminergic neurons' somatodendritic sites and modulate neuronal excitation via membrane depolarization. Because of their presynaptic location in GABAergic and glutamatergic terminal fields, nicotinic receptors in this region play an important role in the regulation of both excitatory and inhibitory input to VTA dopaminergic cells (Alexandris et al., 2021).

Neuromuscular blocking agents (NMBAs), commonly called muscle relaxants or paralytic agents, make an unique group of drugs used during general anaesthesia. In contrast to most other agents administered during general anesthesia, NMBAs do not participate in the administration of sedation, hypnosis, or analgesia, and cross the blood-brain or placental barrier in significant concentrations. NMBA is mostly a hydrophilic compound with limited distribution. Its only effect on skeletal muscle relaxation, which is achieved by interfering with normal neuromuscular transmission. The neurotransmitter released from motor neurons are unable to stimulate skeletal muscles to produce contractions. This specific action renders the patient incapable of producing motor activity, even in response to noxious stimuli (Flores M. M, 2013).

Neuromuscular blocking agents (NMBAs) are the drugs most frequently involved in IgE-mediated anaphylaxis during anesthesia which can lead to perioperative morbidity and mortality. The rate of NMBA anaphylaxis shows marked geographic variation in patients with no previous NMBA exposure, suggesting that there may be external or environmental factors that contribute to the underlying etiology and pathophysiology of the reaction. Substituted ammonium

ions are shared among the NMBAs and are therefore considered to be the main allergenic determinant of the drug class. Substituted ammonium ions are found in a variety of chemical structures, including prescription drugs, over-the-counter drugs and common household chemicals, such as quaternary ammonium disinfectants. Epidemiological studies have shown parallels in the consumption of pholcodine, an over-the-counter antitussive drug containing tertiary ammonium ion, and the incidence of NMBA anaphylaxis. This link has prompted the withdrawal of pholcodine in several countries, with subsequent reductions in NMBA anaphylaxis rates being observed. While such observations are interesting in their suggestion of an association between pholcodine exposure and hypersensitivity (Flores M. M., 2013).

The main objective of including NMBA in the anesthesia protocol is to promote muscle relaxation without need the large doses of general anesthesia. The addition of NMBA to the anesthetic protocol allows the anesthesiologist to administer general anesthesia at a dose just sufficient to provide hypnosis (Flores M. M., 2013).

METHODS

In writing this mini-review was started with literature studies. Originating journal from the *PubMed* database was used by year published since 2012 to 2022. All the articles were relevant to the aim of the research. The keywords are "*ACh Receptor, Neuromuscular Blocking Agents, New Neuromuscular Blocking Drugs and New Neuromuscular Blocking Drugs in ACh Receptors".* Source of primary data obtained from the international and national journals were screened based on title, abstract, and assessment journal in a manner whole. This *literature* review was written based on all the journals studied in a manner thorough.

RESULTS & DISCUSSION

Results

NO.	TITLE	RESULTS
1.	The future of neuromuscular blocking agents. (2020)	Drug development led to the emergence of a series of neuromuscular compounds called chlorofumarates such as gantacurium. The development of this drug has a pharmacodynamic profile with L-cysteine adducts without relevant side effects. The spectrum of the newly discovered agent still in pre-clinical trials is from a modified γ-cyclodextrin derivative that forms inactive inclusions with vecuronium that reverses the neuromuscular steroid blocking agent.
2.	Efficacy of sugammadex in reversing neuromuscular blockade in adults (Efficacy sugammadex in reverse blockade neuromuscular in adults). (2017)	Acetylcholinesterase inhibitors are used to block non-depolarizing neuromuscular transmission. Sugammadex is a selective relaxant binding agent that has been developed for the rapid reversal of recuronium-induced non-depolarizing neuromuscular blockade, as well as for other clinical purposes.
3.	Sugammadex and rocuronium-induced anaphylaxis.	In this study, succinicoline (recuronium use) was associated with higher rates of IgE-

	(2016)	mediated anaphylaxis compared with muscle relaxant agents. Sugammadex is a neuromuscular blocking steroid that is used to reverse the effects of recuronium and vecuronium.
4.	Is Cisatracurium the Neuromuscular Blocking Agent of Choice in Acute Respiratory Distress Syndrome?. (2018)	Cisatrium has several advantages over to other neuromuscular blocking agents, including its ability to eliminate, which is independent of kidney and liver function, and direct anti-inflammatory properties in addition to other neuromuscular blocking effects.
5.	Recuronium. (2022)	Recuronium is a non-depolarizing neuromuscular blocking drug, that is used for muscle relaxation prior to surgery. It is also a non-depolarizing neuromuscular blocking drug with rapid and reversible action.
6.	Non-depolarizing Neuromuscular Blockers (nNMBs). (2022)	In this paper, discuss about the mechanism of action associated with non-depolarizing neuromuscular blockers (nNMBs) such as rocuronium, vecuronium, pancuronium, atracurium, cisatracurium, and mivacurium.
7.	Pancuronium Enhances Isoflurane Anesthesia of Cerebral Nicotinic Acetylcholine Receptors (Pancuronium Upgrade Isoflurane Anesthesia from Receptors Acetylcholine Nicotinic cerebral). (2016)	In the use of pancuronium injection with a dose of the lateral ventricles can depend on the depth of isoflurane anesthesia, due to the inhibition of nicotinic acetylcholine receptors on the nerves in the cerebrum so that the use of high doses can cause an increase in the cerebrospinal region with certain effects.
8.	Cisatracurium Stimulates Testosterone Synthesis in Rat Via Nicotinic Acetylcholine Receptor (Cisatracurium Stimulate Synthesis of Testosterone in Mice Through Receptors Acetylcholine Nicotinic). (2020)	Cisatracurium is the one of cis-acting non-depolarizing neuromuscular blockers through the nicotinic acetylcholine receptor (nAChR), which is often used in anesthetics tested on rat Leydig cells where CAC can increase intracellular cAMP levels (cAMP signal transduction).
9.	Neuromuscular Blocking Agent Cisatracurium Attenuates Lung Injury by Inhibition of Nicotinic Acetylcholine Receptor-α1. (2016)	In this journal is explained the use of NMBA can reduce lung injury by increasing the mechanism of ventilator synchronization and reducing the inflammatory response. NMBAs (Neuromuscular Blocking Agents) will bind to nicotinic acetylcholine receptors, which function in inflammatory signaling. The NMBA plays a role in protecting the lungs because of its anti-inflammatory properties by blocking nAChRα1.
10.	Reversal of Mivacurium-induced Neuromuscular Blockade with a Cholinesterase Inhibitor: A systematic review. (2019)	Mivacurium is a short-acting, non-depolarizing muscle relaxant, that is hydrolyzed by butyrylcholinesterase. NMB (Neuromuscular Block) can be antagonized by cholinesterase inhibitors (CHEI).
11.	Comparative Effectiveness of x-Drugs and Sugammadex to Reverse Non-depolarizing Neuromuscular-blocking Agents (Effectiveness Comparative Medication -x and	Analyzing the relationship between dose and drug response to NMB (Neuromuscular Block) induced by vecuronicum, rocuronium, and cisatracurium which was evaluated in vitro, was illustrated by the curve of the drug neostigmine or sugammadex made ex vivo as well as the dose

	Sugammadex to Agent blocker Non-depolarizing neuromuscular). (2015)	response relationship of the drug tested under conditions of physiological secretion in the urine.
12.	New Drug Developments for Neuromuscular Blockade and Reversal: Gantacurium (Developments Drug New for Blockade and Reversal Neuromuscular: Gantacurium). (2018)	Gantacurium is a neuromuscular management drug that has a rapid onset of action with the addition of l-cysteine and has no side effects, as well as anticholesterase reverse drugs capable of reversing non-depolarizing neuromuscular blocking drugs.
13.	Reversal with Sugammadex in the Absence of Monitoring did not Preclude Residual Neuromuscular Block (Reversal with Sugammadex in the absence Monitoring no Removing Neuromuscular Block residue). (2013)	Sugammadex has a faster and more effective antagonism mechanism than rocuronium-induced neuromuscular blockade. Using neuromuscular monitoring, this multicenter observational study will determine whether sugammadex can reduce the incidence of postoperative residual weakness compared the administration of rocuronium with the antagonists.

DISCUSSION

Neuromuscular inhibitor drugs this not available yet in use clinical however available a number of medium compounds are under development. Draft mechanism pharmacology in clinical with method stimulates transmission neuromuscular afterward track neuromuscular inhibited so that non-depolarizing occurs at the end operation. In theory, both of pharmacological options should restore neuromuscular signal transmission to a TOF greater than 0.9 within 10 minutes, ensuring that extubation goes smoothly. Anticholinesterase drugs prevent acetylcholine from being degraded in the neuromuscular system. However, due to its effects on muscarinic acetylcholine receptors and nicotinic receptors, have a similar effect on non-target tissues and therefore combined with atropine (Sta & Blobner, 2020).

Sugammadex is a selective drug to reverse the effects of rocuronium induced neuromuscular blockade. Sugammadex has some disadvantages, including the possibility of allergic reactions and the risk of postoperative bleeding (Takazawa et al., 2016).

Gantacurium is a class of acetylcholine-nicotinic receptor blockers because it binds to endogenous L-cysteine and permanently inactivates neuromuscular signaling. It is a chemically asymmetric, enantiomeric isoquinolinium diester of chlorofumaric acid. Gantacurium hemodynamic studies revealed an increase in plasma histamine levels. Gantacurium metabolism is sensitive to pH hydrolysis and involves the adduction action of cysteine. Gantacurium-induced neuromuscular signaling pathway blocking occurs spontaneously. Exogenous L-cysteine may hasten recovery from gantacurium-induced neuromuscular blockade. Gantacurium is a non-depolarizing neuromuscular blocking agent with an antagonistic mechanism of action to cholinesterase inhibitors. Edrophonium is a short-acting anticholinesterase that is less potent than neostigmine, but it is only effective during neuromuscular recovery. The time to reversal of the gantacurium-induced block after edrophonium administration was 3.8 minutes (at 10% recovery, a T1 to TOF ratio of 0.90), compared to 5.7 minutes for spontaneous reversal of the same block.

Exogenous L-cysteine antagonism, on the other hand, proved to be superior to anticholinesterases. Gantacurium acts similarly to succinylcholine, but with fewer side effects, due to its fast onset and metabolism (Sta & Blobner, 2020).

Sugammadex is a combination drug rocuronium and a selective neuromuscular antagonist, which is have great potential because sugammadex's effective for neuromuscular inhibition and the postoperative prevention of pulmonary complications. Sugammadex inhibits rocuronium-induced neuromuscular blockade. However, the Food and Drug Administration (FDA) has denied drug approval due to the possibility of allergic reactions and postoperative bleeding. However, this drug was eventually approved to treat hypersensitivity and anaphylactic reactions. Sugammadex is a modified g-cyclodextrin with a lipophilic can coat other lipophilic molecules (Sta & Blobner, 2020).

Cyclodextrins are carbohydrate cyclic oligosaccharides composed of eight sugar molecules derived from starch degradation. Cyclodextrins are designed to bind to rocuronium and a lesser extent, other steroidal muscle relaxants such as vecuronium and pancuronium. After sugammadex injection, neuromuscular function returns in two stages. The first step is to package all free intravascular molecules of rocuronium in the central compartment following an intravenous injection of sugammadex. As a result, there is a concentration gradient down the neuromuscular pathway. The extravasal rocuronium molecules are then transferred from the neuromuscular junction to the intravasal, central compartment, where they are encapsulated. The kidneys metabolize nearly 100% of the drug, with a clearance of 75-120 ml/min. Sugammadex exposure is increased in patients with moderate (creatinine clearance 30-50 ml/min) and severe (creatinine clearance 30ml/min) renal impairment due to the gradual decrease in creatinine clearance. Sugammadex at a dose of 4 mg/kg was well tolerated in subjects with renal impairment in a phase study. Sugammadex dose adjustment is not required in patients with moderate renal impairment, according to these findings. Sugammadex was tested in patients with renal failure, and the mean time to recovery of the TOF ratio in the renal failure group (5.6 3.6 min) was 0.9 longer than in the control group (2.7 1.3 min, P140.003). There were no side effects or evidence of recurrence from neuromuscular blockade in this study (Sta & Blobner, 2020).

Cisatracurium increased oxygenation and decreased inflammation in young children when tested for the mechanism of neuromuscular blockade in acute respiratory distress syndrome (ARDS). ACURASYS (ARDS et Curarisation Systematique) trial in France 2010 tested cisatracurium for 48 hours in 340 patients with ARDS and found improved 90-day adjusted survival without evidence of worsening muscle weakness. Neuromuscular blocking agents have also been shown to help patients with sepsis and respiratory infections. Cisatracurium has a high potential as a neuromuscular blocking agent because it has independent elimination from kidney and liver function, no active metabolite, and a short half-life. Cisatracurium has anti-inflammatory properties are distinct from neuromuscular blocking effect (Shaykhiev et al., 2018).

After cisatracurium, vecuronium is the commonly used neuromuscular blocking agent. Two tests were performed to determine the duration of neuromuscular blockade in patients who received vecuronium therapy and patients

who received cisatracirium. he test results revealed, there wasn't significant difference in the risk of mortality between these two drugs (Shaykhiev et al., 2018).

Neostigmine and edrophonium were given during post-therapy to accelerate mivacurium-induced NMB recovery. Neostigmine administered when T1 ≥ 5% accelerated the reversal time by up to 6.5 minutes. After 5 minutes, neostigmine has a small effect. This effect was not clarified in deep mivacurium-induced NMB in adults. Edrophonium given to mivacurium-induced NMB accelerates the reversal time, in adults by about 9 minutes. Six out of ten studies found an effect at least 6 minutes. The minimum treatment time for T1 5% effect is 6 minutes. Plasma levels per unit time were observed for detection of muscle contraction in response to PTC up to T1 = 25%. Doses of neostigmine ranged from 0.02 to 0.07 mg/kg, while edrophonium doses ranged from 0.5 to 1 mg/kg. Edrophonium is most effective when given at a T1 <5%. Use of edrophonium accelerated reversal by a maximum of 9.2 minutes in contrast to 6.5 minutes when using neostigmine. It is likely that neostigmine antagonism overcomes BChE inhibition at about a 5% T1. When T1 was 5%, neostigmine and edrophonium sped up mivacurium-induced NMB recovery times in adults about 5-6,5 and 6-9 minutes. In deeper NMB (T < 5%) edrophonium accelerated recovery, whereas its effect wasn't clarified for neostigmine in adults (Takazawa et al., 2016).

Metabolism and Cholinesterase Enzymes

Neuromuscular blocking metabolites shouldn't have neuromuscular blocking effects; however, the nature of the NMBDs (New Neuromuscular Blocking Drugs) must be considered. Recuronium's 1% metabolized will be extensively broken down by NMBDs, shortening its duration. Mivacurium is broken down by plasma cholinesterase, whereas atracurium and cisatracurium are broken down by Hofmann elimination and ester hydrolysis (Kim, Y. B., et al 2017).

The cholinesterase enzyme degrades ACh, which is released through the neuromuscular synaptic cleft. Mivacurium and succinylcholine metabolism will be affected in the presence of abnormal plasma cholinesterase activity. There is no effect on ACh synthesis in the neuromuscular, but its degradation becomes slower and will increase the concentration of ACh and causing a change in neuromuscular blockade. NMBDs (New Neuromuscular Blocking Drugs) can also inhibit plasma and erythrocyte cholinesterase. The inhibition can be competitive, non-competitive, and reversible, or it can involve decreasing and increasing the concentration of ACh. Except when mivacurium is degraded by plasma cholinesterase, this cholinesterase inhibitory effect has an effect on NMBD expression (Kim, Y. B., et al 2017).

CONCLUSION

Neuromuscular blocking agents were originally introduced in 1942 in anesthesia. Blocking agents are administered for anesthetics and used for muscle paralysis that may facilitate endotracheal intubation. Drugs belonging to the neuromuscular blocking agents are Sugammadex, Gantacurium, Edrophonium, Rocuronium, Cyclodextrin, Vecuronium, and Pancuronium. These drugs are used as muscle relaxants or muscle relaxants during surgery. The cholinesterase enzyme is an enzyme that can degrade Ach which has been released through the

neuromuscular synaptic cleft. NMBDs (New Neuromuscular Blocking Drugs) can also hinder plasma and erythrocyte cholinesterase. There is an effect of cholinesterase enzyme on the expression of neuromuscular blocking drugs (NMBD) that is passed through a neuromuscular blockade. Mivacurium and Succinylcholine will have an impact on ACh concentrations.

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