MODULATING MUSCLE ACTIVITY USING GABA INHIBITORS

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ABSTRACT

Introduction: Overuse of muscles, stress and dehydration are some of the reasons for muscle spasms. Muscle cramps often resolve on their own but in some cases medical intervention is required.

Aim: The aim of this article is to study the modulating muscle activity using GABA inhibitors.

Materials and Methods: Treatment plans for bruxism include different ways for modulating muscle activity, which should be studied.

Results: A spasm is an involuntary, unexpected contraction of one or more muscles. Muscle spasms can happen in any muscle of the human body. The most common reasons for the occurrence of spasms are overuse of a muscle, dehydration or stress.

Discussion: Gamma-aminobutyric acid (GABA) serves as the main inhibitory neurotransmitter in the developed, mature central nervous system of mammals. $GABA_A$ receptors are ligand-activated chloride chan-nels. GABA receptors are the main focus of this study because of their wide spread throughout the mam-malian nervous system. In a recent study from 2017, Gervasi, Sisti and team from Baltimore discovered that the regular application of thiocolchicoside-based foam topically on *m. rectus et biceps femoris* reduced the risk of muscle cramps, muscle pain and improved the overall performance of the athletes in the study group.

Conclusion: This discovery, along with the known properties of thiocolchicoside and its structure, present an interesting perspective when considering new ways to treat muscle spasms. Dermal patches ensure the gradual release of a substance in a certain area through the skin. The idea is to develop a dermal patch for application on *m. masseter et temporalis* when treating patients with bruxism.

Keywords: *muscle activity, inhibitors, GABA, GABA receptors, cycling, local application, bruxism*

INTRODUCTION

Overuse of muscles, stress, and dehydration are some of the reasons for muscle spasms. Muscle cramps often resolve on their own but in some cases medical intervention is required. One example is bruxism—a condition known to medical doctors, dentists, and even people, whose profession has nothing to do with medicine.

AIM

The aim of this article is to study the modulating muscle activity using GABA inhibitors.

MATERIALS AND METHODS

Treatment plans for bruxism include different ways for modulating muscle activity, creating a schedule for muscle use, making sure the masticatory muscles are not in constant tension, introduction

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of myorelaxants. These can be applied through injecting in a particular site, orally, or topically. In the following article the main focus will be on topically applied myorelaxants and their use in treating bruxism.

RESULTS

Muscle spasm. A spasm is an involuntary, unexpected contraction of one or more muscles (1). It is also known as cramp or a twitch. Muscle spasms can happen in any muscle of the human body. The most common reasons for the occurrence of spasms are overuse of a muscle, dehydration, or stress. Most of the times no medical attention is required as this condition can resolve on its own. However, in some cases, the muscle can be relaxed only through the use of physiotherapy or myorelaxants. These can be taken orally as pills, or applied locally through injection or topical gel.

In order for a molecule to be able to pass through the skin, it has to meet certain requirements:

- lypophillic;
- hydrophilic;
- below 500DA in size;
- weak ionization.

DISCUSSION

What is GABA? Gamma-aminobutyric acid (GABA) serves as the main inhibitory neurotransmitter in the developed, mature central nervous system of mammals. GABA is capable of reducing neuronal excitability in all parts of the nervous system.

Neurons producing GABA are known as GABAergic, and have inhibitory role at reception in adult vertebrate organisms. In insects, however, they serve both an excitatory and inhibitory role, conducting signals for muscle contraction at neuro-muscular synapses, as well as stimulation of glands (2). Some GABAergic neurons in mammals, like chandelier cells, are also capable of transmitting activation signals to their glutamatergic counterparts (3).

$GABA_A$ receptors. GABAA receptors are chlorine channels activated by a ligand: when activated by GABA, they let chloride ions flow across the cell membrane (4). When the net flow of chloride is decreasing within the cell, GABA is depolarizing; when the amount of chloride in the cell is increasing, GABA is inhibitory or hyperpolarizing. When chlorine is neither flowing in or out of the cell, GABA is shunting. Shunting inhibition does not directly change the the membrane potential of the cell; it decreases the strength of any coincident synaptic input by increasing the electrical conductivity of the membrane of the cell. Shunting inhibition can inhibit the excitatory effect of depolarizing GABA. As a result, overall inhibition occurs even if the membrane potential becomes more positive. During the brain development to adulthood, GABA's role switches from excitatory to inhibitory (5).

Inhibition mechanism. The endogenous ligand of the GABAA receptor is γ-aminobutyric acid—the most wide spread neurotransmitter in the mammalian central nervous system. When opened, the GABAA receptor exhibits selective permeability to chloride ions (Cl–), and to bicarbonate ions (HCO3–) to a lesser extent (6,7). The direction of ionic flow across the pore depends on the potential of the membrane and the difference in ionic concentration. An example: under normal physiological conditions, the flow of Cl– is directed into the cell if the electrical potential of the membrane is above the equilibrium potential (reversal potential) when the GABAA receptor is active (8). This phenomenon leads to a decreased chance of an action potential occurrence at the postsynaptic cell—inhibition of transmitting electrical signal.

GABAA receptors comprise of five subunits, arranged around a transmembrane pore. Each subunit is made of four transmembrane domains with extracellular location of both the N- and C- terminus. The GABAA receptor is located in the membrane of its neuron, in most cases postsynaptically at the synapse. Some isoforms may be located outside the synapse (9). Whenever GABA vesicles are released presynaptically and activate the GABA receptors at the synapse, the phenomenon is known as phasic inhibition. If, however, the GABA vesicles escape the synaptic cleft and activate GABA receptors outside the synapse of the same neuron or adjacent neurons ("spillover") this is added to the constant low GABA extracellular concentration and leads to the persistent activation of the GABAA receptors, known as tonic inhibition (10).

Why target GABA receptors? GABA receptors are the main focus of this study because of their wide spread throughout the mammalian nervous system. Their activation mechanism is studied and well known, which makes the choice of a competitive, reversible inhibitor easier.

Such inhibiting agent is thiocolchicoside—a myorelaxant with anti-inflammatory and analgesic effects.(11–14) It acts as a competitive GABAA receptor antagonist as well as glycine receptor antagonist with resembling potency and nicotinic acetylcholine receptors to a lesser extent (15,16). It has powerful convulsant activity and is not recommended to seizure-prone individuals (17–19).

In a recent study from 2017, Gervasi, Sisti and team from Baltimore discovered that the regular application of thiocolchicoside-based foam topically on m. rectus et biceps femoris reduced the risk of muscle cramps, muscle pain, and improved the overall performance of the athletes in the study group (20).

CONCLUSION

This discovery, along with the known properties of thiocolchicoside and its structure, make it an interesting perspective when considering new ways to treat muscle spasms. Dermal patches ensure the gradual release of a substance in a certain area through the skin. The idea is to develop a dermal patch for application on m. masseter et temporalis when treating patients with bruxism.

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