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Serotonin (5-HT) Modulation Model Of Motor Neuron Firing Patterns

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Abstract:
Background*: This study presents a computational model of a motoneuron incorporating the 5-HT1$_a$ serotonin receptor and a presynaptic neuron that releases serotonin (5-HT) upon stimulation. The model aims to elucidate the role of serotonin in motor function and its impact on motoneuron excitability. Three key aspects are analyzed: the relationship between 5-HT1$_a$ receptor density and firing frequency, the effect of varying 5-HT concentrations on motoneuron activation, and the inhibition of Na^+ inward currents during depolarization.*
Materials and Methods*: NEURON software version 8.2 was used for the simulations, employing the CNEXP numerical integration method with a fixed time step of 0.025 ms. This model consists of a multi-compartmental cable model, with anatomical data corresponding to a cat motoneuron. Specific membrane resistivity and capacitance were assigned, and action potentials were generated through Hodgkin-Huxley type active currents. 5-HT1$_a$ receptors were added to motoneuron initial segment for the inhibitory response.*
Results*: Results indicate that increased receptor density correlates with reduced firing rates, while higher concentrations of 5-HT enhance motoneuron activation. Additionally, the release of 5-HT significantly inhibits Na^+ inward currents, leading to a decrease in action potential generation and muscle contraction strength, which contributes to central fatigue.*
Conclusion: *This model provides insights into the complex interactions between serotonin and motoneuron function, with implications for understanding motor-related disorders.*
Keyword*: Motoneurons, Serotonin, 5-HT1$_a$ Receptor, Central Fatigue.*

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I. Introduction

Motoneurons are the final common output of the central nervous system. Their cell bodies located in the brainstem and the ventrolateral part of the spinal cord send axons that connect muscle fibers. Each time a motor neuron generates action potentials, it induces the contraction of the muscle fibers it innervates and therefore triggers a movement. For this reason it is possible to correlate the activity of individual motoneurons with motor control, one of the most important functions of the central nervous system [1]. On the other hand, serotonin (5-HT) is one of the main neuromodulators in the central nervous system. In the adult spinal cord, 5-HT primarily originates from neurons belonging to the raphe spinal pathway. 5-HT is released on different types of neurons, and these include motoneurons, where has a role in motor function [2]. Several studies suggest that 5-HT has a direct effect on motoneurons; in fact, it is known that these neurons express at least 5 subtypes of its receptors: 5-HT1$_a$, 5-HT1$_b$, 5-HT2$_a$, 5-HT2$_b$, 5-HT2$_c$. Furthermore, the application of 5-HT near its membrane increases excitability by modulating various types of conductance (GK, GNa, GCa) and facilitates hyperpolarization activated by cationic current [3]. However, some studies suggest that 5-HT also exerts an inhibitory effect characterized by hyperpolarization and increased membrane conductance. "In vivo" studies suggest that intravenous injection of tryptophan (the precursor amino acid of 5-HT) or directly into the central nervous system accelerates fatigue that occurs during motor activity.

Additionally, the time until exhaustion is decreased by agonists of 5-HT receptors and increases when antagonists are added [4]. How could the same neurotransmitter enhance motoneuron activity and, therefore, muscle contraction while also enhancing fatigue? During movement, motoneurons receive descending and peripheral synaptic impulses that depolarize the membrane and induce the genesis of action potentials. If we assume that the release of 5-HT correlates positively with motor activity, as several studies suggest, this indicates that 5-HT during moderate physical activity facilitates muscle contraction by increasing motoneuron gain through the modulation of various conductances (GK, GNa, GCa) through 5-HT2$_a$ receptors [1]. In contrast, during more intense activity, more 5-HT is released, and reuptake mechanisms become saturated. As a result of the high concentration of 5-HT, it would activate its receptors 5-HT1$_a$ present in the initial segment of

motoneuron axons [5,6]. Here, 5-HT1_a receptors are activated and induce inhibition of action potential initiation and therefore do not allow subsequent muscle contraction. This is the first identified cellular mechanism for central fatigue, a form of motor fatigue that does not depend on muscle tissue [7]. Its function could be to ensure the rotation of motor units during prolonged contractions [8] and prevent muscle hyperactivity [9]. Therefore, the aim of this work is to present a model of motoneuron response inhibition induced by 5-HT.

II. Material And Methods

The model consists of a motoneuron and a generic presynaptic neuron that releases the neurotransmitter 5-HT upon stimulation.

Simulation software

For the development of the modeling, NEURON software version 8.2 was used. This software is a simulation environment for modeling individual and network neurons, which provides a range of conventional tools for constructing, managing, and using modeling in a numerically robust and computationally efficient manner [10]. All simulations were performed using the numerical integration method (CNEXP) built in the NEURON with a fixed time step (0.025 ms) ensuring the stability and accuracy of simulations while varying parameter values in a wide range. The NEURON files of the motor neuron model developed in this study are publicly available at: https://github.com/JGMG7/Serotonin-5-HT-Modulation-Model-of-Motor-Neuron-Firing-Patterns

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Motoneuron

The model of motoneuron proposed by Kim [11] was used as the basis. The model used in the present study were obtained from ModelDB [12]; accession number 235769. This model consists of a multi-compartmental cable model, with anatomical data corresponding to a cat motoneuron (i.e., v_e_moto6), which is available in the public database (www.neuromorph.org). The non-uniform-specific membrane resistivity was assigned to the soma (Rm, soma = 225 Ω cm^2) and the dendrites (Rm, dendrita = 225 Ω cm^2). The specific membrane capacitance (Cm = 1μF/cm^2) and axial resistivity (Ri = 70 Ω cm) were uniformly assigned to all compartments of the motoneuron model. Action potentials and after hyperpolarization phenomena were generated by various Hodgkin-Huxley-type active currents: a fast-inactivating sodium current (INaf), a delayed rectifier potassium current (IKDr), a persistent sodium current (INap), N-type calcium current (ICaN), and calcium-dependent potassium current [IK(Ca)] at the soma and INaf, INap, and IkDr at the initial segment/axonal hillock. Plateau potentials were produced by persistent inward currents (ICaL) mediated by low-threshold L-type Cav1.3 channels in the dendrites. The voltage gated L-type Ca^{++} channel was placed over dendritic sites that were separated by 500–700 μm from the soma. The peak conductances for active currents were GNaf = 0.71 [S/cm^2], GKDr = 0.23 [S/cm^2], GCaN = 0.013 [S/cm^2], and GK(Ca) = 0.0258 [S/cm^2] at the soma, GNaf = 2.7 [S/cm^2], GNap = 0.033 [mS/cm^2], and GKDr = 0.17 [S/cm^2] at the initial segment/axon hillock, and GCaL = 1.37 [mS/ cm^2] in the dendrites. The equations and parameter values for steady-state activation and kinetics of individual active currents can be found in Kim [11]. To generate the inhibitory response of the motoneuron, receptors 5-HT subtype 5-HT1_a were added in the initial segment [5].

5-HT1_a receptor

The 5-HT1_a receptors were designed based on the kinetic response of G protein coupled membrane receptors, which modulate ionic channels [13]. The model used in this study was an adaptation from ModelDB [12]; accession number 18198. The values of the association constants (ka) and dissociation (kd) used to model the 5-HT1_a receptor were calculated from the average of the inhibition constant (ki) values reported in the literature [14].

Presynaptic neuron

The presynaptic neuron is a generic neuron whose function is to release the neurotransmitter upon a stimulus (IClamp). It contains Na^+ channels (3 states) and K^+ channels (2 states) voltage-dependent, following a Markov model [15]. The model used in the present study were obtained from ModelDB [12]; accession number 18198. It is assumed that after the arrival of the action potential, the presynaptic terminal depolarizes and Ca^{++} enters the terminal, giving rise to a high-threshold Ca^{++} current, then the Ca^{++} ions activate the calcium-binding protein, which promotes the release of the neurotransmitter (5-HT) from the presynaptic vesicles into the synaptic cleft. The presynaptic vesicles are considered inexhaustible and always available to be released. This process is modeled as first order with a stoichiometry coefficient of n. The entry of calcium into the presynaptic terminal is modeled by a high-threshold Ca^{++} current, using the same 2-state Markov scheme of the K^+ channel, with a voltage-dependent rate similar to the K^+ current. The intracellular removal of Ca^{++} is promoted by an active transport (calcium pump) [15].

Stimulation protocols

The stimulation consisted of 3 types of input protocols. a) Intracellular stimulation in the soma, which is a StepIClamp (0.5 nA, -0.3 nA, 0.27 nA y 0.3 nA; on1 =100 ms, on2 = 300 ms, on3 = 500 ms, on4 = 950 ms; off1 = 130 ms, off2 = 330 ms, off3 = 900 ms, off4 = 980 ms) with duration of 1000 ms and current of 3 nA amplitude (Fig.1a). b) Synaptic excitation in the dendrites (Fig. 1b), which is achieved through variations in the conductance of excitatory synapses located in these segments, where L-type Cav 1.3 channels were positioned. It could be assumed that it is being partly facilitated by the activation of the 5-HT2$_a$ receptors described previously [1]. c) Intracellular stimulation in the presynaptic neuron through IClamp with duration of 28 ms, current 0.1 nA and delayed of 500 ms (Fig. 2 a).

Neurotransmitter release

From the stimulus applied to the presynaptic neuron, the release of approximately 10 mM of the neurotransmitter (5-HT) is estimated (Fig. 2b). Considering that 10 mM = 0.01M.

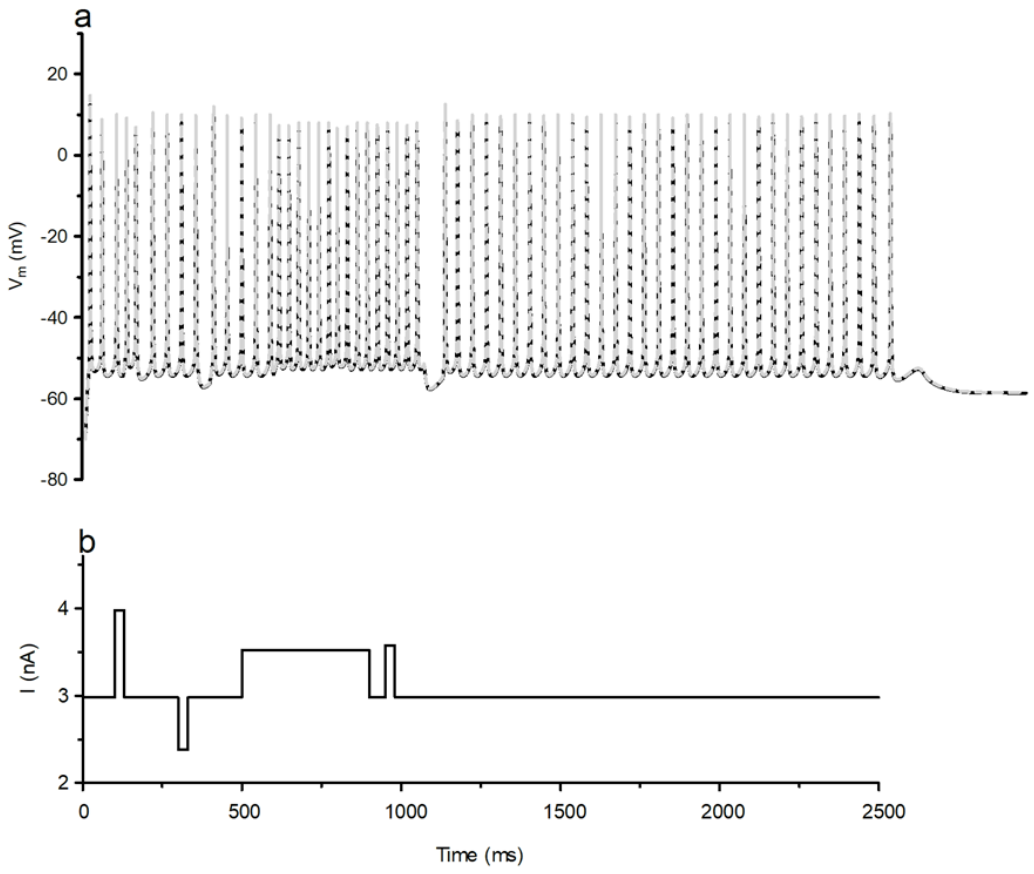
Motoneuron Inhibition

Upon depolarization of the presynaptic neuron and the subsequent release of 5-HT with a delay of 500 ms, the inhibition of the motoneuron response is observed, despite receiving stimulation through the StepIClamp in the soma and the excitatory synapses in the dendrites (Fig. 3).

Graphics

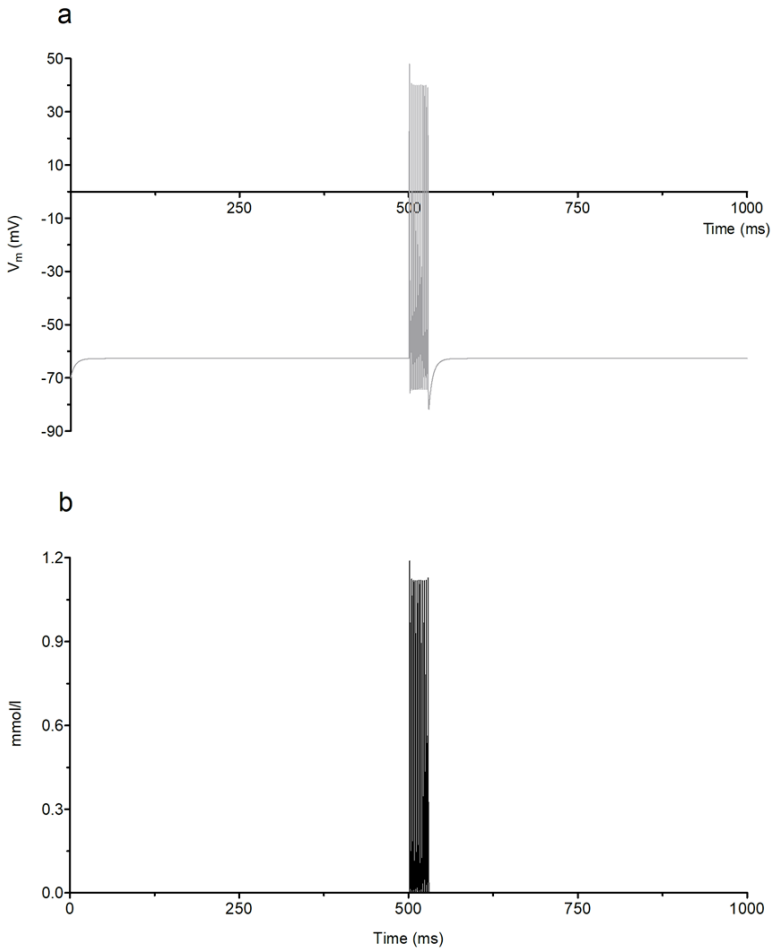
The displayed graphs have been created from the data obtained from the simulations carried out in NEURON version 8.2 and subsequently processed and designed in Python version 3.8.

Fig. 1



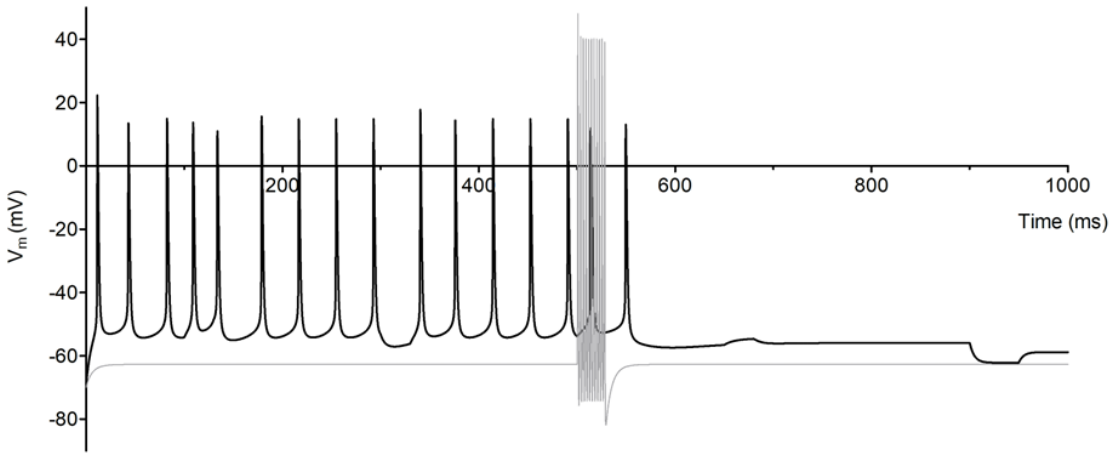
Motoneuron stimulation a) Response of soma (dotted gray trace) to StepIClamp and dendrite [310] response (solid black trace) to both StepIClamp and dendritic excitatory synapses. The firing rate (~ 29 Hz). Which is enough to cause a muscle contraction. StepIClamp pattern applied to soma (b).

Fig. 2



Presynactic neuron stimulation (a). The trace shows the firing of the presynaptic neuron, in response to the input (IClamp) applied in this case with a delay of 500 ms. Neurotransmitter release (b). Release of 5-HT after each firing of the presynaptic neuron (firin rate ~ 39 Hz).

Fig. 3



Inhibition of motoneuron firing after to apply IClamp in the presynaptic neuron with 500 ms delay, and neurotransmitter release. Black trace (initial segment actions potentials), gray trace (presynaptic neuron actions potentials).

III. Result

In this chapter, we present the results of the computational modeling of a motoneuron with the 5-HT1$_a$ serotonin receptor. Three key aspects are analyzed: first, the relationship between 5-HT1$_a$ receptor density and firing frequency is evaluated, highlighting how this density modulates neuronal excitability. Second, the impact of different 5-HT concentrations on motoneuron activation. Finally, the Na^+ inward current in the initial segment of the motoneuron during depolarization and its inhibition by serotonin.

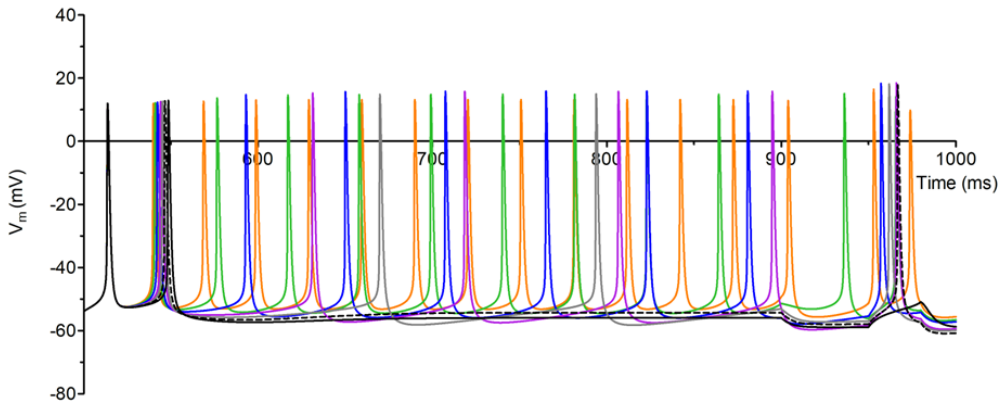
5-HT1$_a$ receptors density

Different amounts of the 5-HT1$_a$ receptor were added to the initial segment of the motoneuron, with the intention of understanding the relationship between the receptor density and the modulation of the firing frequency (Fig. 4).

5-HT concentration and firing rate

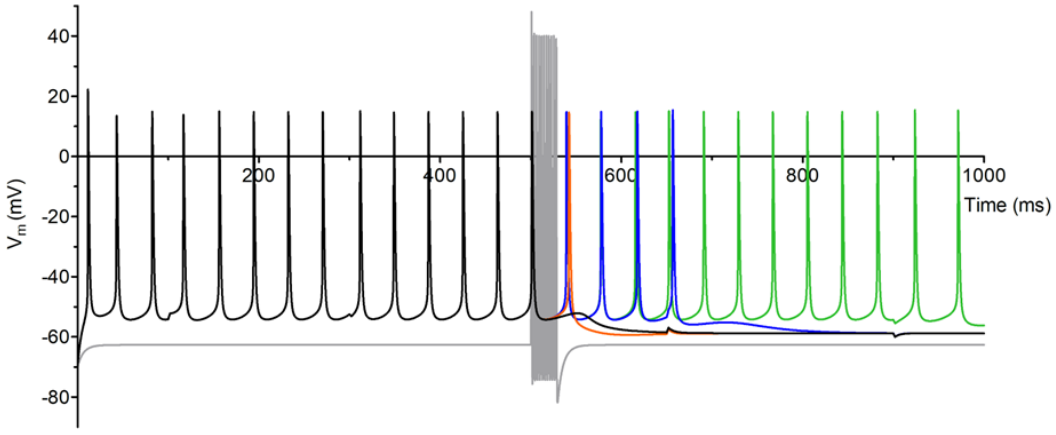
The concentration of 5-HT released by the presynaptic neuron was modified with each stimulation to determine how these changes modulate motoneuron activation. The density of 5-HT1$_a$ receptors was maintained at 500 (Fig. 5).

Fig. 4



Firing frequencies of motoneurons with different densities of the 5-HT1$_a$ receptor: 50 (orange), 150 (green), 250 (blue), 350 (purple), 400 (gray), 450 (dotted black trace), and 500 (solid black trace) receptors in the initial segment, after the neurotransmitter (5-HT) has been released at 500 ms.

Fig. 5

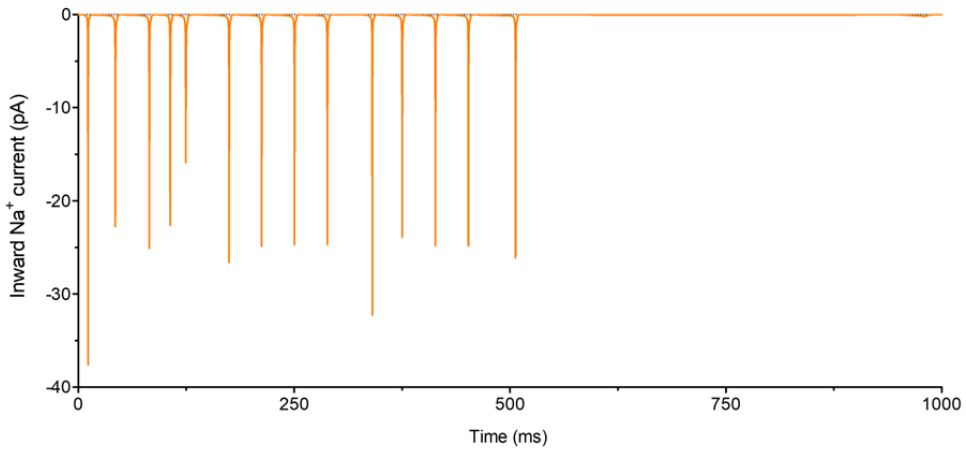


Relationship between the concentration of 5-HT released into the synaptic space and its modulation of motoneuron activation. The gray trace represents the firing of the presynaptic neuron that induces the release of 5-HT. The green trace represents motoneuron activation in the presence of 0.01 mM 5-HT. The blue trace represents motoneuron activation in the presence of 0.1 mM 5-HT. The orange trace represents motoneuron activation in the presence of 1 mM 5-HT. The black trace represents motoneuron activation in the presence of 10 mM 5-HT.

Initial segment inward Na^+ current inhibition

Following the inhibition generated by the release of 5-HT, the inward Na^+ currents that are activated during motoneuron depolarization are also drastically reduced (Fig. 6).

Fig. 6



Inhibition of inward Na^+ current, after to apply IClamp in the presynaptic neuron with 500 ms delay. Orange trace represent Na^+ inward current.

IV. Discussion

This study involves a motoneuron model that incorporates 5-$HT1_a$ receptors and presynaptic neuron releasing 5-HT. The model is designed to gain a deeper understanding of the role of serotonin in the nervous system and its impact on motor function. Serotonin is a neurotransmitter involved in modulating motor activity, and it has been shown that the activation of 5-$HT1_a$ receptors results in an inhibition of the response. This research provides valuable insights into the complex interactions between neurotransmitters and motor function. During intense physical exertion, an increased amount of serotonin is released. The reuptake mechanisms become saturated, causing serotonin to overflow and reach the extrasynaptic 5-$HT1_a$ receptors located on the motoneurons initial segment.

This is possible because the initial segment lacks serotonergic innervation [5]. This subsequently triggers the inhibition of the Na^+ channels that are crucial for the commencement of action potentials. As a result of the inhibition of the Na^+ channels, fewer nerve impulses are produced, leading to a reduction in muscle contraction strength. This decrease in motoneuron gain, induced by serotonin, initiates a state of central fatigue [6]. This is a fascinating aspect of how our bodies regulate physical exertion at the cellular level.

A relevant aspect of cellular signaling is related to receptor density. In particular, it has been reported that 5-$HT1_a$ receptors have a considerably high density in the spinal cord [16]. Our model's results suggest that the effect of high serotonin concentrations on the initial segment of motoneurons is linked to the density of these receptors.

Notably, when the density of 5-$HT1_a$ receptors is increased from 50 to 500 units in the initial segment, a decrease in firing rate is observed (Fig. 4). The differential expression of the 5-$HT1_a$ receptor among groups of motoneurons might explain the variability in responses to serotonin addition across neuronal populations, where the reactions to the neurotransmitter are markedly heterogeneous. This differentiated effect of serotonin on motoneuron populations, based on the equally differentiated expression of the 5-$HT1_a$ receptor, appears to be a reasonable strategy for modulating the neurotransmitter's impact on motoneuron activation.

In experimental studies, 5-HT-induced inhibition on the action potential (AP) genesis of motoneurons was achieved by adding 15 mM of Serotonin [5]. To achieve similar inhibitory effect on motoneuronal firing in our model, it is sufficient to induce the release of at least 0.1 to 10 mM of 5-HT from a presynaptic neuron (Fig. 5).

On the other hand, Na^+ inward currents are fundamental in neuronal depolarization processes, enabling the transmission of signals essential for muscle contraction and other motor functions [17]. In this model, it can be observed how the release of 5-HT inhibits these Na+ inward currents, thus emulating the effect of the 5-$HT1_a$ receptor activation (Fig. 6).

Finally, the results of this model align with findings related to the role of serotonin in modulating motor activity through the activation of 5-$HT1_a$ receptors [1]. Therefore, this model could be useful for gaining a deeper understanding of the mechanisms involved in this modulation.

V. Conclusion

The proposed model can be used to simulate different serotonin concentrations and their impact on motor activity, which can be valuable for studying serotonin-related diseases such as Parkinson's disease, depression, or the side effects associated with the use of serotonin reuptake inhibitors [18]. However, it is important to consider its limitations, such as the lack of consideration for other factors that may influence motor activity, including the presence of dopamine and norepinephrine.

In future research, we aim to increase the model's complexity to include catecholamine receptors, other serotonergic receptors, and factors associated with cellular metabolism, such as pH and temperature. Despite these limitations, we are aware that this is the first proposed model concerning this mechanism of muscle fatigue.

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