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Computational Modeling of Aβ Fiber Wind-up

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Abstract— **Wind-up, a condition related to chronic pain, is described traditionally as a frequency dependent increase in the excitability of sensory spinal cord neurons, evoked by electrical stimulation of small pain fibers. In this paper, we introduce a computational model on wind-up of large (Aβ) fibers, considering three major mechanisms of wind-up:**

1) a feedforward mechanism causing Ca2+ entry, 2) a positive feedback, causing more Ca2+ entry, and 3) a feedforward due to sprouting of Aβ fibers towards the small pain fibers.

Our model proposes three different ways for reducing wind-up and shows the most important way to treat the pain.

I. Introduction

RATIONAL treatment of chronic pain depends on increased understanding of the pathophysiological mechanisms underlying the various characteristics of chronic pain, among which central sensitization has received great attention in recent years. The experimental models used to explore mechanisms of central sensitization include the study of wind-up in animals and temporal summation of pain in humans. Temporal summation of repeated painful stimuli has been regarded as a psychophysical correlate of wind-up in humans [1].

Wind-up is described traditionally as a frequency dependent increase in the excitability of spinal cord neurons, evoked by electrical stimulation of afferent C-fibers [2]. However, researchers have proposed different kinds of wind-up. Wind-up of dorsal horn neurons is usually evoked by C-fiber and occasionally by Aδ-fiber stimulation [3]. A novel type of wind-up has been evoked by stimulation of Aβ fibers in hyperalgesic states induced by peripheral injury or inflammation [4].

Several authors have reviewed the electrophysiological and behavioral data indicating a significant role of NMDA (N-methyl-D-aspartate) receptor in wind-up [5, 6]. There are two main molecular mechanisms involved in this regard. We have described these mechanisms as feedback and feedforward processes in our last paper [7]. Our hypothesis, trying to analyze Aβ wind-up, consists of three main parts (Fig. 1): 1- an extra feedforward mechanism causes Ca^{2+} entry, 2- a positive feedback, causing more opening of NMDA receptors and hence more Ca^{2+} entry, and 3- sprouting of Aβ fibers towards the C fibers. In the present study, we model this hypothesis and present a computational model, which is compatible with empirical results.

II. Methodology

In order to conduct the simulation and observing the dynamics we use a cosine shaped curve of order 8, used by [8, 9], as the wind-up impulse train; $x_{input}=2.5\cos^8(2\pi t)$.

As each synapse, causes approximately 0.5ms delay in action potential propagation, so the delay between direct stimulation of Aβ fibers and sprouting stimulation of C fibers is supposed 0.5ms.

Two major mechanisms appear to contribute to the resultant increased synaptic efficacy: (1) alterations in ion channel and/or receptor activity owing to posttranslational processing that we call it "the dynamics of the system", and (2) trafficking of receptors to the membrane, which we model it as a DC gain [10].

Considering our block diagram (Fig. 1), we have mentioned four building blocks, G_1 to G_4, which introduce two major mechanisms of calcium inward current (G_1 and G_2), dynamics of calcium transmission through the cell membrane (G_3), and a calcium feedback loop (G_4).

The feedforward process G_1 is modeled as a low pass filter with τ =0.1, which represents the dynamic of unblocking Mg^{2+} from NMDA receptors, with DC gain of K=0.8.

$$G_1 = \frac{0.8}{0.1s+1} \qquad (1)$$

Activation of AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors and other Ca^{2+}

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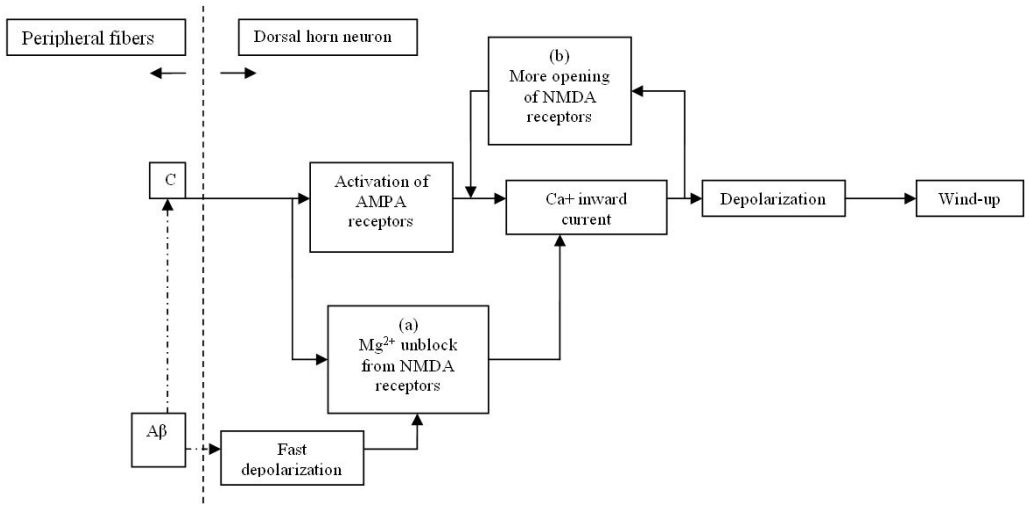


Fig. 1. Block diagram of wind-up from cybernetic point of view. (a) is the feedforward process, and (b) is the feedback. The sprouting of Aβ fibers is shown by dashed arrows.

channels, with a slower dynamics compared to G_1, can be represented as:

$$G_2 = \frac{2}{0.2s+1}. \qquad (2)$$

As the number of NMDA receptors is less than other Ca^{2+} channels and receptors, we presumed larger DC gain for G_2.

The above-mentioned mechanisms activate the inward calcium current in the dorsal horn neuron. This, in part, causes depolarization of cell membrane and more opening of NMDA receptors, which can be modeled as a positive feedback with G_4 dynamics. For simplicity, we assume the gain is a constant. Rate of cytosolic calcium concentration change $\dot{y}$ depends on inward ion current from G_1 and G_2, (x), as well as outward current through ion pumps:

$$\tau \cdot \dot{y} = Kx - y \qquad (3)$$

Hence,

$$G_3 = \frac{1}{s+1}. \qquad (4)$$

Since wind-up is the result of the cytosolic Ca^{2+} concentration (y), it can be assumed as the output of the model. Figure (2-a) shows the whole model, as implemented in Simulink, MATLAB 7.

III. Results

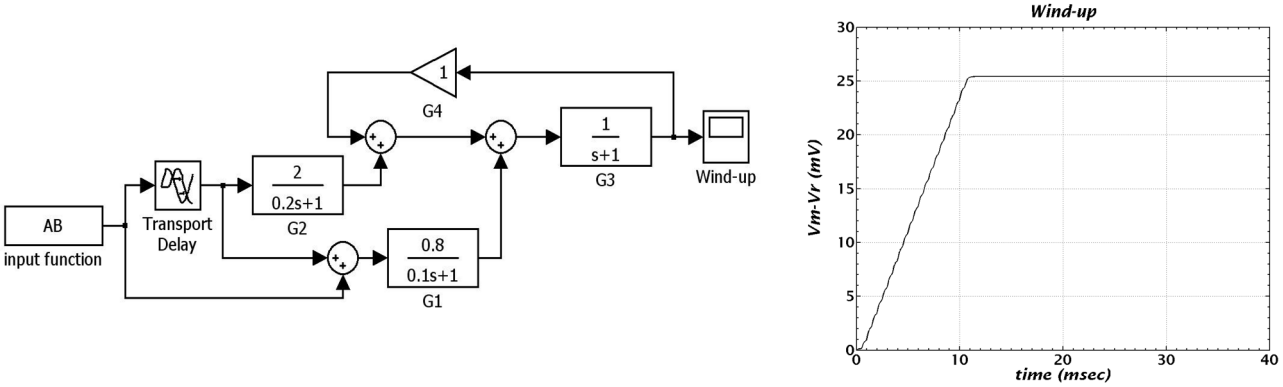
The wind-up signal is shown in fig (2-b). The input of the system has amplitude of 2.5mv, but the output, difference between membrane voltage and resting voltage (V_m-V_r) is about 25mv. This voltage stays constant for seconds, resembling a potentiation that can be assumed as wind-up.

Examining different parts of our hypothesis lead to interesting results:

1- If we do not consider the sprouting phenomenon, V_m achieves to -64.4mv (Fig. 3). Hence no wind-up occurs.

2- Excluding NMDA receptors (both the feedback and feedforward loops), V_m changes a little, about 1.5mv, indicating the importance of NMDA receptors in producing wind-up.

3- Our model shows that blocking other receptors and channels that contribute to Ca^{2+} inward current, has less



(a) (b)

Fig. 2. (a) Wind-up model implemented in Simulink MATLAB 7. (b) Wind-up signal in response to applied stimulation.

effect on relieving wind-up than NMDA receptor blockage (V_m-V_r = -58.8mv).

IV. Discussion and Conclusion

The above-mentioned results show that:

1- Sprouting phenomenon may have a remarkable effect on wind-up. We have hypothesized previously the role of Aβ fibers in wind up, through sprouting of nerve fibers in the dorsal horn of spinal cord and named it ''sprouting phenomenon''[11]. It has been reported that in some clinical hyperalgesic states induced by peripheral injury or inflammation, wind up may aggravate the pain. For example, studies have indicated the presence of wind up in postsurgical states, some neuropathic pains, fibromyalgia syndrome, and post-herpetic neuralgia. It seems that our present model partly validates our hypothesis, although future clinical studies are needed to confirm it.

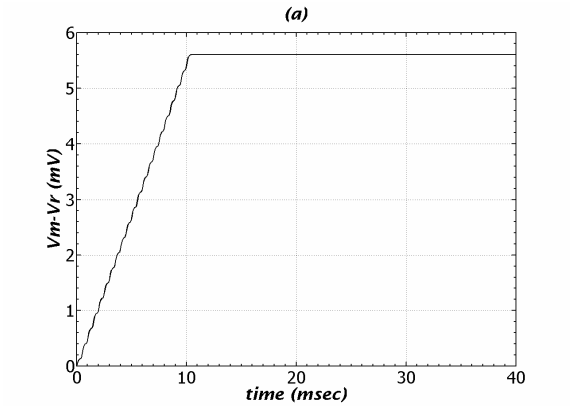


Fig. 3. (a) Slashing the sprouting connections to C fiber. Difference between membrane voltages (mv) with the normal rest potential is plotted versus time (ms).

2- NMDA receptors have major role in wind-up and blocking them by increasing extracellular Mg^{2+} can relieve wind-up [12, 13].

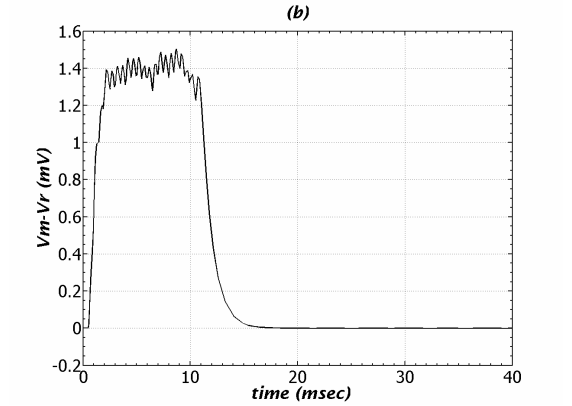


Fig. 3. (b) Plotting the output voltage, considering no NMDA receptors, shows the importance of these receptors.

3- The effect of other Ca^{2+} channels in wind-up is mentioned in different experiments [14, 15], but we think it has minor effect compare to the NMDA receptors.

Since the real transfer functions of G_1 and G_2 are not known, we changed them, to see if our hypothesis about their dynamics (time constant) and trafficking (DC gain) is correct. We observed that DC gain is more effective than the time constants.

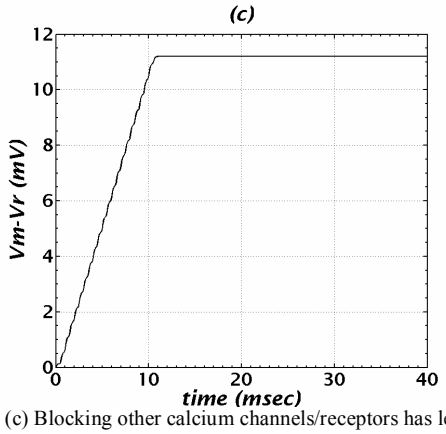


Fig. 3. (c) Blocking other calcium channels/receptors has less effect compared to disconnection of sprouting pathways or blockage of NMDA receptors.

Considering our computational model, some clinical interventions can be assessed to alleviate post-inflammatory pains: (1) Immediate relief of inflammation by anti-inflammatory agents to prevent repetitive excitation of C-fibers and subsequent morphological changes of dorsal horn laminae; (2) using local anesthetics in order to prevent pain signal transmission; (3) prevention of sprouting by intrathecal injection of some anti-proliferation agents; (4) using NMDA antagonists to prevent central mechanism of wind up [16]. Certainly experimental researches are needed to validate the benefits of our suggestions in relieving such clinical pains.

Presenting more detailed models for wind-up, may help the scientists to study the pain more definitely and propose better pain relief methods. We hope this research could be a trigger for these useful studies.

References

[1] Eide, P. K., "Wind-up and the NMDA receptor complex from a clinical perspective," European Journal of Pain, 2000; 4: 5–17.

[2] Herrero JF, Laird JM, Lopez-Garcia JA, "Wind-up of spinal cord neurons and pain sensation: much ado about something?," Prog Neurobiol, 2000; 61(2):169-203.

[3] Price, D.D., Hull, C.D., Buchwald, N.A., "Intracellular responses of dorsal horn cells to cutaneous and sural nerve A and C fiber stimuli," Exp Neurol, 1971; 33, 291-309.

[4] Thompson, S.W.N., Dray, A., Urban, L., "Injury-induced plasticity of spinal reflex activity: NK1 neurokinin receptor activation and enhanced A- and C-fiber mediated responses in rat spinal cord in vitro," J Neurosci, 1994; 14, 3672-3687.

[5] Dickenson A., "Mechanisms of central hypersensitivity: excitatory amino acid mechanisms and their control," In: Dickenson A, Besson JM, editors. The Pharmacology of Pain. Berlin: Springer Verlag, 1997; 167–210.

[6] Willis WD, Sluka KA, Rees H, Westlund KN., "Cooperative mechanisms of neurotransmitter action in central nervous sensitization," Prog Brain Res, 1996; 110: 151–166.

[7] Farajidavar A.,gharibzadeh S., Towhidkhah F., Saeb S., "A cybernetic view on wind-up," Med Hypotheses, 2006; 67, 304-306.

[8] Britton, N.F., Chaplain, M.A.J. and Skevington, S.M. 1996, "The Role of N-methyl-D-aspartate (NMDA) Receptors in Wind-up: A Mathematical Model," IMA J Math Appl Med Biol, 1996 Sep;13(3):193-205.
[9] Prince K., Campbell J., Picton P., Turner S., "A computational model of acute pain," I. J. of Simulation, Vol. 6 No 9, ISSN 1473-804x online, 1473-8031 print.
[10] Woolf, C.J. and Salter, M.W. "Neuronal plasticity: increasing the gain in pain," Science 288, 2000, 1765–1769.
[11] Hoseini SS, Hoseini MS, Gharibzadeh S. "Sprouting phenomenon, a new model for the role of A-beta fibers in wind up," Med Hypotheses, 2006;66(4):805–7.
[12] Bhatia A, Kashyap L, Pawar DK, Trikha A., "Effect of intraoperative magnesium infusion on perioperative analgesia in open cholecystectomy," J Clin Anesth., 2004; 16(4):262-5.
[13] Seyhan TO, Tugrul M, Sunger MO, Kayacan S, Telci L, Pembeci K, Akpir K. "Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery," Br J Anaesth , 2006; 96(2):247-52.
[14] Miljanich GP, "Ziconotide: neuronal calcium channel blocker for treating severe chronic pain," Curr Med Chem., 2004; 11(23):3029-40.
[15] Silverman R, Bendick PJ, Wasvary HJ. "A randomized, prospective, double-blind, placebo-controlled trial of the effect of a calcium channel blocker ointment on pain after hemorrhoidectomy," Dis Colon Rectum., 2005; 48(10):1913-6.
[16] Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. "Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome," Pain, 2001;91(1–2):165–75.