



## A cybernetic view on wind-up

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**Summary** 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. Different kinds of wind-up have been reported, but wind-up of A $\beta$  fibers in hyperalgesic states has gained little attention. In this paper, we present a cybernetic view on A $\beta$  fiber wind-up and consider the involved molecular mechanisms as feedback and feedforward processes. Furthermore, our previous hypothesis, the sprouting phenomenon, is included in this view. Considering the proposed model, wind-up in hyperalgesic states might leave out in three different ways: (1) blocking the NMDA receptors by increasing extracellular Mg<sup>2+</sup>, 2) blocking the receptors and channels that contribute to Ca<sup>2+</sup> inward current, and 3) blocking the A $\beta$  fibers by local anesthetics. It seems that wind-up may be inhibited more effectively by using these three blocking mechanisms simultaneously, because in this case, the feedback process (main controller), the feedforward process (trigger), and A $\beta$  stimulation (trigger) would be inhibited concurrently.

Wind up may aggravate the pain in clinical hyperalgesic situations such as post-surgical states, some neuropathic pains, fibromyalgia syndrome, and post-herpetic neuralgia. Surely, clinical studies are needed to validate the effectiveness of our abovementioned suggestions in relieving such clinical pains.

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### 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 [4].

Wind-up is described traditionally as a frequency dependent increase in the excitability of spinal

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cord neurons, evoked by electrical stimulation of afferent C-fibers. Although it has been studied over the past 30 years, there are still uncertainties about its physiological meaning [5].

Several authors have reviewed the electrophysiological and behavioral data indicating a significant role of NMDA receptor in wind-up [3,16]. There are two main molecular mechanisms involved in this regard:

- (a) Thompson et al. [13] have proposed that during repetitive stimulation, each stimulus would find the cell at a more depolarized membrane potential and this may contribute to the removal of the  $Mg^{2+}$  block from the NMDA receptors. The progressive release of the  $Mg^{2+}$  block would further increase the intracellular calcium [13].
- (b) Chen and Huang [2] have proposed a secondary amplification mechanism dependent upon  $Ca^{2+}$  entry via the NMDA ionophore or other  $Ca^{2+}$  channels during the depolarization. An increase in intracellular  $Ca^{2+}$  would activate protein kinase C (PKC) and this in turn, would increase further the efficacy of NMDA receptors [2,5].

It is worth noting that different kinds of wind-up have been proposed by researchers. The wind-up of dorsal horn neurons is usually evoked by C-fiber and occasionally by  $A\delta$ -fiber stimulation [9]. A novel type of wind-up has been evoked by the stimulation

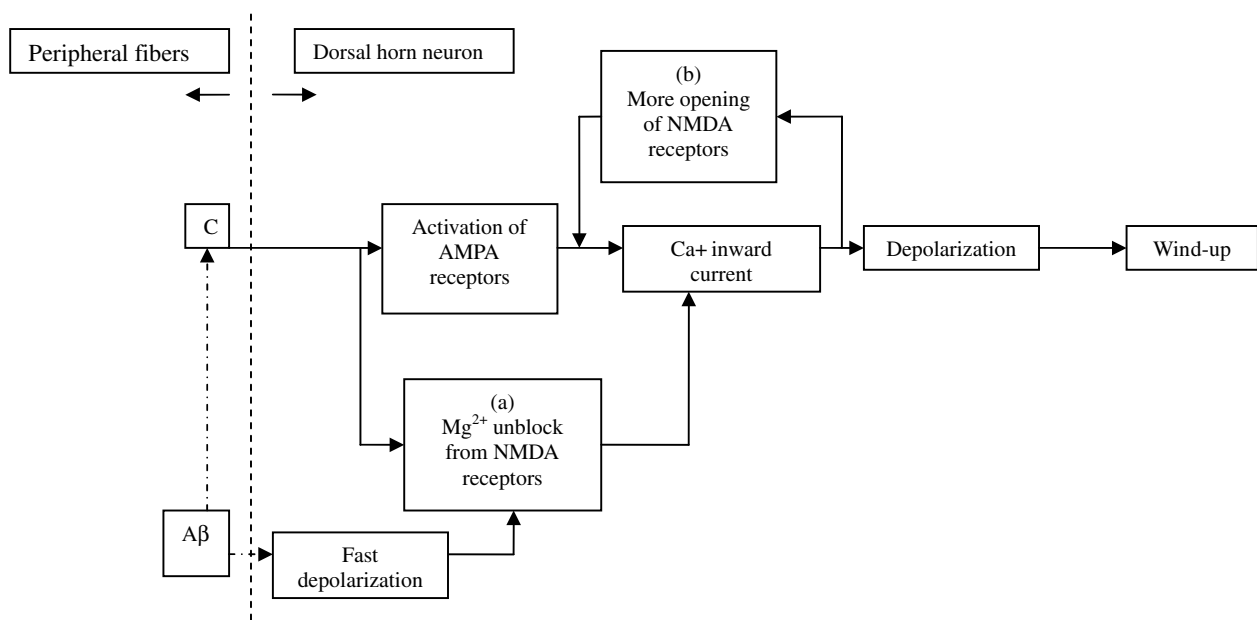
of  $A\beta$  fibers in hyperalgesic states induced by peripheral injury or inflammation [14]. A new hypothesis of  $A\beta$  wind-up claims that, after nerve injury or inflammation for at least 20 h,  $A\beta$  fibers sprout to more superficial lamina where they may contact nociceptive neurons [7].

Using these mechanisms, we conclude a new hypothesis, which mainly focuses on  $A\beta$  wind-up.

## The hypothesis

Our hypothesis, trying to examine wind-up with a cybernetic point of view, consists of three parts:

- 1) As shown in Fig. 1, considering the wind-up events as a control system, the mechanism (a) (proposed by Thompson) may be regarded as a feedforward process. This mechanism, as well as the activation of AMPA receptors, causes  $Ca^{2+}$  entry into the dorsal horn neurons. In cybernetics, feedforward is usually for triggering and predicting [6].
- 2) In Fig. 1, the mechanism (b) (proposed by Chen and Huang) may be considered as a positive feedback, because increment of cytosolic  $Ca^{2+}$  affects the NMDA receptors and opens them more, and consequently more  $Ca^{2+}$  would flow inward. In cybernetic view, a positive feedback causes instability of system [15].



**Figure 1** Block diagram of wind-up from cybernetic point of view (a) is the feedforward process, and (b) is the feedback. The sprouting of  $A\beta$  fibers is shown by dashed arrows.

- 3) Since in hyperalgesic states, A $\beta$  fibers probably sprout towards the C fibers, A $\beta$  fiber stimulation activates C fibers and simultaneously triggers mechanism (a). C fibers in turn activate both feedback and feedforward loops. In other words, sprouting strongly activates the whole system.

We think that all above mechanisms cooperatively produce the wind-up and omitting each of them can noticeably affect the pain intensity.

### Consequences of the hypothesis

Considering the proposed model, wind-up in hyperalgesic states might leave out in three different ways:

- 1) Blocking the NMDA receptors by increasing extracellular Mg<sup>2+</sup>. Some experimental studies have shown evidences about pain relief by this method [1,10].
- 2) Blocking the receptors and channels that contribute to Ca<sup>2+</sup> inward current. Some experimental researches indicate the importance of this analgesic method [8,11].
- 3) Blocking the triggering system (A $\beta$  fibers) in order to suppress the whole system. To do so, we need local anesthetics that block cutaneous stimulations. Similar experiments have done by Herrero et al. [5], which applies lidocaine directly into the spinal cord.

It seems that wind-up may be inhibited more effectively by using the three blocking mechanisms simultaneously, because in this case, the feedback process (main controller), feedforward process (trigger), and A $\beta$  stimulation (trigger) would be inhibited concurrently.

Wind up may aggravate the pain in some clinical hyperalgesic states induced by peripheral injury or inflammation. For example, studies have indicated the presence of wind up in post-surgical states, some neuropathic pains, fibromyalgia syndrome, and post-herpetic neuralgia [12]. Certainly experimental researches are needed to validate the benefits of our suggestions in relieving such clinical pains.

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