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Primary Afferent Depolarization and the Gate Control Theory of Pain: A Tutorial Simulation

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The gate control theory of pain postulates that the sensation of pain can be reduced or blocked by closing a "gate" at the earliest synaptic level in the spinal cord, where nociceptive (pain) afferents excite the ascending interneurons that transmit the signal to the brain. Furthermore, the gate can be induced to close by stimulating touch afferents with receptive fields in the same general area as the trauma that is generating the pain (the "rub it to make it better" effect).

A considerable volume of research has substantiated the theory and shown that a key mechanism mediating the gate is pre-synaptic inhibition, and that this inhibition is generated by depolarizing IPSPs in the nociceptor central terminals (primary afferent depolarization; PAD).

Both pre-synaptic inhibition and depolarizing IPSPs are topics that students often regard as matters of secondary importance (if they are aware of them at all), and yet they are crucial to a matter of primary importance to us all – pain control. This report describes some simple computer simulations that illustrate pre-synaptic inhibition and explore the importance of the depolarizing aspect of the IPSPs. These concepts are then built into a model of the gate control of pain itself. Finally, the simulations show how a small change in chloride homeostasis can generate the dorsal root reflex, in which nociceptor afferents generate antidromic spikes which may increase neurogenic inflammation and actually exacerbate pain. The hope is that the simulations will increase awareness and understanding of a topic that is important in both basic neuroscience and medical neurology.

Key words: pain, gate control theory, pre-synaptic inhibition, PAD, primary afferent depolarization, dorsal root reflex, simulation, computational neuroscience

We all know from personal experience that relatively minor pain, such as that caused by an insect sting or a stubbed toe, can be relieved by rubbing the affected area. We also know, although for most of us, thankfully, not from personal experience, that even the pain from major trauma can be somewhat reduced by similar means. After the British admiral Nelson was mortally wounded at the battle of Trafalgar (1805), eyewitnesses reported him as repeatedly saying "Drink, fan, rub ..." in the hours before he died. Presumably the mechanical stimulation of being rubbed to some extent alleviated his pain. It is therefore evident that the experience of pain is not a simple and inevitable result of the activation of pain (nociceptive) afferents, but rather is subject to numerous modulating factors that can diminish or increase it. Since the experience of pain is usually unpleasant, sometimes extremely so, it is not surprising that a lot of research has been conducted to better understand how it can be diminished even while the physical insult that causes the pain is still present.

One of the earliest and most influential theories regarding pain modulation is the "gate control theory" (Melzack and Wall, 1965). This postulates that the pain pathway can be interrupted at the very first synaptic level—the one connecting nociceptive afferent output in the dorsal horn of the spinal cord with the ascending projection interneurons that transmit the sensation to the brain. It is as though there were a gate at the synapse, and if the gate is shut, the afferents simply cannot pass their signal on to the interneurons. Furthermore, the gate can be shut either by stimulating non-nociceptive afferents from the body surface near the damaged tissue (the "rub it to make it better" effect), or by descending control from higher brain regions (e.g., the battle rage that can sometimes enable even severely wounded soldiers to continue to fight).

The theory of a spinal gate in the pain pathway has been largely substantiated by subsequent research, and a key mechanism is thought to be pre-synaptic inhibition (see Comitato and Bardoni, 2021, for a recent review). Nociceptive (and other) afferent central terminals have $GABA_A$ receptors at or near their transmitter release sites in the dorsal horn, and there is a population of GABAergic interneurons in that region that can activate these receptors and thus reduce transmitter release. These inhibitory interneurons can themselves be activated by touch-sensitive neurons from near the region generating the pain. One of the interesting features of the inhibition is that although the IPSPs are mediated by an increase in conductance to chloride, they are all *depolarizing*. This is because the afferent neurons have an unusually high intracellular chloride concentration, leading to a chloride equilibrium potential which is depolarized relative to the resting potential. The general effect is known as primary afferent depolarization, or PAD.

For undergraduate students, pre-synaptic inhibition can sometimes seem like a rather obscure "poor relation" compared to post-synaptic inhibition, where the role of competitive summation of EPSPs and IPSPs in decision-making is intuitively obvious. And the role of depolarizing

IPSPs seems even more anomalous. Depolarization takes a neuron closer to threshold, so how can it be inhibitory? To help students understand these phenomena and their role in modulating pain, I developed some simple computer simulations that explore these topics. These could be used either by a tutor as animated illustrations in a standard lecture/tutorial session, or they could be given to students in a laboratory setting with instructions for an appropriate set of experimental activities (such as those that generated the results described below).

MATERIALS AND METHODS

The simulations were constructed using the low-cost commercial Windows program Neurosim (https://www.st-andrews.ac.uk/~wjh/neurosim/; Heitler, 2022), because that program was specifically designed with student use in mind. All the figures in this report are screenshots taken from the program, enabling a user's-eye view of the output. Similar simulations can undoubtedly be constructed using freely-available research-oriented tools such as Genesis (2019) or Neuron (2021), but these tools have a steeper learning curve and are arguably less suitable for the non-expert user.

The simulations make simplifying assumptions because their aim is to allow the user to explore the underlying concepts, rather than to produce realistic (research level) simulations of specific physiological data. Key simplifications relevant to this project are listed below.

1. All spikes are generated using parameters from the original Hodgkin-Huxley (1952) model of the squid giant axon operating at 6°C, rather than from mammalian neurons operating at their body temperature. This is partly because the squid spikes are exemplars of general spike features that are widely used in teaching, and partly because there simply is not an equivalent level of detail available for all the various mammalian neural sub-types involved in the circuit.
2. To model pre-synaptic inhibition at the excitatory afferent-to-interneuron synapse mediating pain transmission ('a' in Figure 1), the transmission needs to be sensitive to the shape of the pre-synaptic spike. This was achieved in Neurosim by specifying the synapse as a "non-spiking" type (despite the fact that the afferent is definitely spiking) because this allows the post-synaptic conductance (g mS/cm^2) to be an instantaneous function of the pre-synaptic membrane potential (v mV):

$$g = 0.5 / (1 - \exp((25 - v) / 4)$$

   This sigmoidal function has an effective threshold of about 0 mV and saturates at about +50 mV. This means that the post-synaptic conductance is sensitive to the amplitude and duration of the pre-synaptic spike, but only within this voltage window, which encompasses the peak of the spike.

   In real neurons, this effect is mediated by changes in the activation of pre-synaptic calcium channels, leading to changes in calcium inflow and hence changes in transmitter release, but these intermediate steps are not included in the simulation.
3. The synapse mediating pre-synaptic inhibition in the afferent terminal (i.e., the gate control; 'b' in Figure 1)) is specified in Neurosim as a "spiking" type in which the post-synaptic conductance rapidly increases by 4 mS/cm^2 when the membrane potential of the inhibitory interneuron crosses 0 mV during the rising phase of its spike, and then declines exponentially with a time constant of 10 ms. It thus decays to zero over about 55 ms.

Instructions for running the simulations described in the Results, including links to ready-built Neurosim parameter files and a student-friendly version of the paper, are provided in the supplementary material.

RESULTS

This report describes 2 related models. The first deals with pre-synaptic inhibition mediated by PAD, while the second illustrates how this inhibition works in the gate control of pain.

Pre-Synaptic Inhibition through PAD

The simulation setup (Figure 1) includes an afferent neuron whose central terminal receives inhibition from a pre-synaptic inhibitory interneuron. The afferent excites an ascending interneuron. The afferent and inhibitory neurons support Hodgkin-Huxley-type spikes but the ascending interneuron is passive. The latter simplifying (and obviously unrealistic) property allows the afferent-generated EPSP to

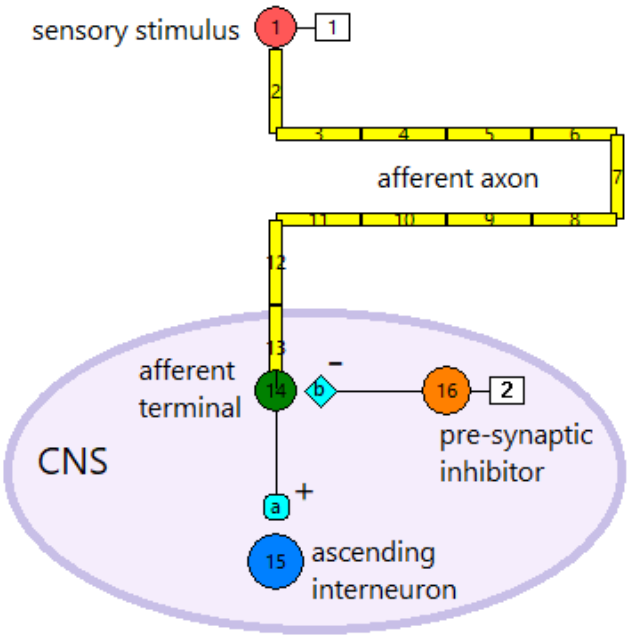

Figure 1 Simulating pre-synaptic inhibition of an afferent neuron. The afferent receptor (red circle 1) receives an external stimulus (square box 1), and its non-myelinated axon (compartmental model, yellow rectangles 2-13) transmits spikes to the dorsal horn of the spinal cord (CNS). The afferent terminal (green circle 14) makes an excitatory synapse (cyan rounded rectangle a) to an ascending projection interneuron (single compartment, blue circle 15), but the terminal itself can receive depolarizing inhibitory input (cyan diamond b) from the pre-synaptic inhibitor interneuron (single compartment, orange circle 16) if the latter is stimulated (square box 2). The figure is a screenshot from the Neurosim Setup view.

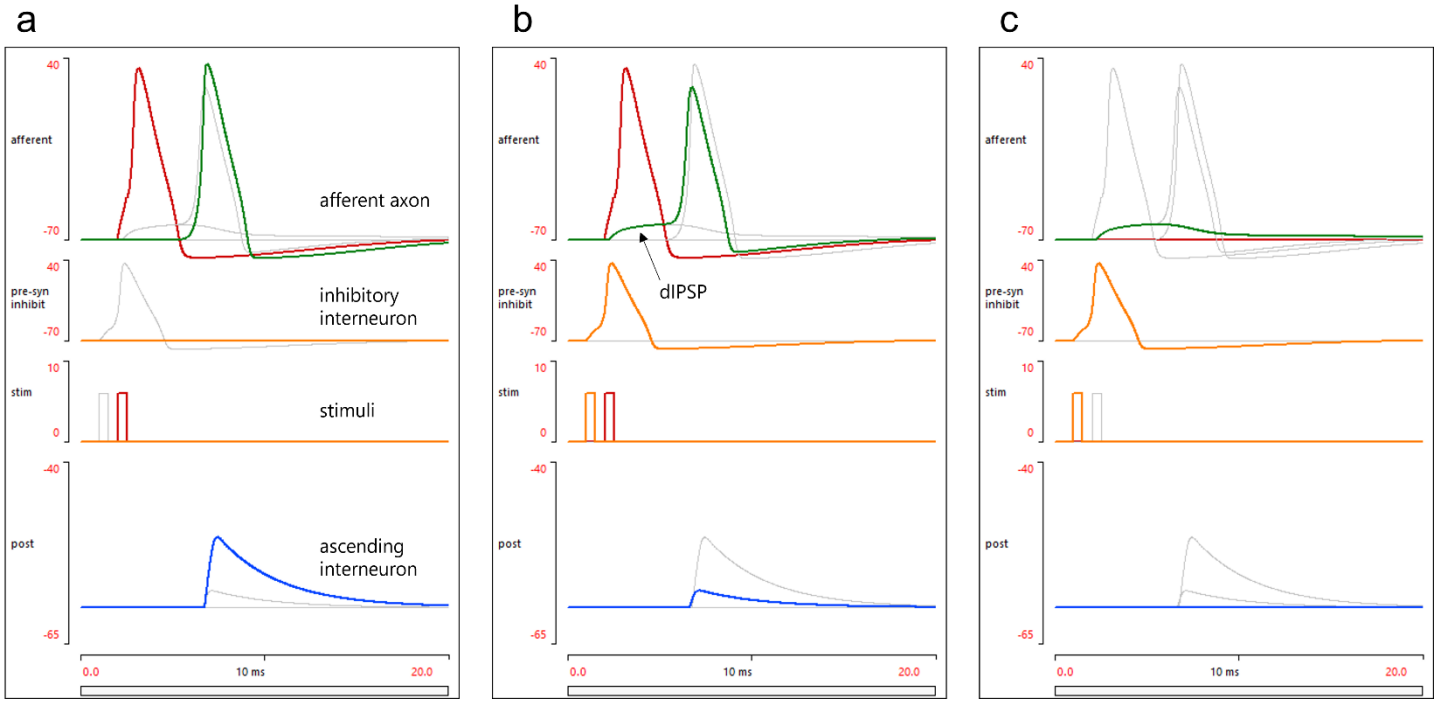

Figure 2. Primary afferent depolarization can mediate pre-synaptic inhibition. Each panel shows the same 3 superimposed sweeps, but the sweeps are highlighted in turn, with the non-highlighted sweeps shown in grey for comparison. *a.* The afferent is stimulated *without* activating the pre-synaptic inhibitor. *b. Both* the afferent and the inhibitor are stimulated. *c.* The inhibitor is stimulated without stimulating the afferent. Top axis: The afferent peripheral receptor compartment (red trace, red circle 1 in Figure 1) and central terminal compartment (green trace, green circle 14). Second axis: The pre-synaptic inhibitor (orange trace, orange circle 16). Third axis: The stimuli applied to the peripheral receptor and pre-synaptic inhibitor. Bottom axis: The EPSP generated in the ascending interneuron (blue trace, blue circle 15). Note that stimulating the pre-synaptic inhibitor generates a depolarizing IPSP (dIPSP) in the afferent terminal which then has reduced spike amplitude and width, leading to a reduced post-synaptic EPSP. The figure panels are screenshots from the Neurosim Results view.

be seen without contamination by any spike-related responses.

When the peripheral afferent receptor is stimulated it generates a spike that propagates along its axon and into the CNS. Here it makes excitatory synaptic output onto the ascending interneuron, where it generates an EPSP (Figure 2a). If the pre-synaptic inhibitory interneuron is stimulated just before the afferent spike reaches its terminal, the terminal receives a long-duration depolarizing IPSP (dIPSP) and its spike is reduced in both amplitude and duration. Consequently, the EPSP in the post-synaptic interneuron is significantly reduced in amplitude (Figure 2b). Stimulating the inhibitor alone generates the dIPSP, but this is normally subthreshold and does not trigger a spike in the afferent terminal, so the ascending interneuron is unaffected (Figure 2c).

It is entirely plausible that the full-size EPSP (without pre-synaptic inhibition; Figure 2a) could be above threshold in the ascending interneuron and therefore generate a spike, while the reduced-size EPSP (with pre-synaptic inhibition; Figure 2b) would fail. Thus, pre-synaptic inhibition mediated by primary afferent depolarization can indeed in principal act as a gate in the transmission path of sensory information to the brain.

Shunting or Inactivation/Activation?

There is no doubt that pre-synaptic inhibition exists in real nervous systems, and there is also no doubt that it is often mediated by PAD. There is some doubt, however, about the exact mechanism causing the inhibition. There are two plausible and non-mutually exclusive possibilities: shunting and activation/inactivation of voltage-dependent channels.

Inhibition through shunting occurs because the increase in chloride conductance during the IPSP will tend to pull the membrane potential of the afferent terminal towards the chloride equilibrium potential, and so will reduce peak spike amplitude and the activation of voltage-dependent calcium channels, and hence reduce the release of transmitter. This will occur whether the IPSP is depolarizing, silent, or hyperpolarizing. However, depolarizing IPSPs allow another possibility – partially pre-inactivating voltage-dependent sodium and/or calcium channels and partially activating voltage-dependent potassium channels before the afferent spike arrives at the central terminal. This will reduce and shorten the afferent spike in the terminal, and thus also reduce transmitter release.

The simulation allows the two mechanisms to be distinguished by altering the equilibrium potential of chloride in the afferent, without altering the conductance change underlying the IPSP (Figure 3).

It is clear in the simulation that the depolarizing aspect of the IPSP makes a significant contribution to the inhibitory effect. Inhibition mediated by the IPSP when the chloride equilibrium potential is depolarized relative to the afferent

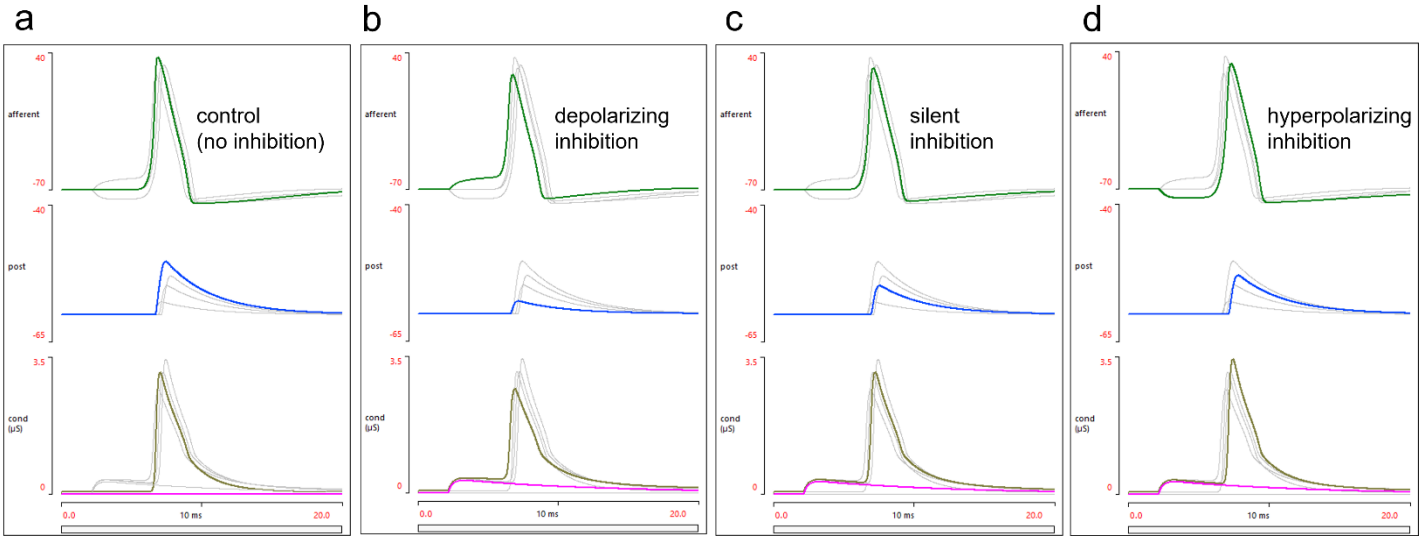

Figure 3. The relative importance of shunting and depolarization in mediating pre-synaptic inhibition through PAD. Each panel shows the same 4 superimposed sweeps, but the sweeps are highlighted in turn, with the non-highlighted sweeps shown in grey for comparison. *a.* The control condition with no pre-synaptic inhibition. *b.* Pre-synaptic inhibition with a depolarizing IPSP (chloride equilibrium potential = -61 mV). *c.* Pre-synaptic inhibition with a silent IPSP (chloride equilibrium potential = -70 mV, which is the afferent resting potential). *d.* Pre-synaptic inhibition with a hyperpolarizing IPSP (chloride equilibrium potential = -80 mV). Top axis: The membrane potential in the afferent central terminal compartment (green). Second axis: The EPSP in the ascending interneuron (blue). Bottom axis: The chloride conductance mediating the IPSP (magenta) and the total membrane conductance (khaki) in the afferent terminal. Note that the chloride conductance is identical in b-d.

resting potential produces the smallest EPSP in the ascending interneuron compared to control with no inhibition (Figure 3a *vs* 3b). Shunting does, however, also make a significant contribution. When the chloride equilibrium potential is set equal to the resting potential, the IPSP is silent (i.e., it produces no change in afferent membrane potential) but there is still a reduction in the afferent terminal spike amplitude due to the increased chloride conductance, and consequently a reduction in the EPSP in the ascending interneuron (Figure 3a *vs* 3c). The EPSP is larger, however, than that which occurs with depolarizing inhibition, so the shunting inhibition alone is less effective than when it is combined with depolarizing inhibition (Figure 3 b *vs* 3c). Finally, the IPSP can be given a more conventional hyperpolarizing waveform by setting the chloride equilibrium potential negative to afferent resting potential. In this case there is only a slight diminution in EPSP amplitude compared to control (Figure 3a *vs* 3d), so this is the least effective form of pre-synaptic inhibition of them all.

We thus have a plausible explanation for why pre-synaptic inhibition of afferent terminals in the spinal cord is mediated by PAD – it is more effective than shunting alone (the silent IPSP), and considerably more effective than a conventional hyperpolarizing IPSP. This is presumably because the depolarization affects the voltage-dependent channels in the afferent terminal.

The role of voltage-dependent channel activation and inactivation can be further investigated in simulation by looking at the channel gate open probability variables (*m*, *h* and *n*) of the channels themselves. (Note that the term “gate” here refers to the molecular conformation changes controlling the opening and closing of voltage-dependent channels – it has nothing to do with the gate control theory.) These gates are, of course, constructs of the Hodgkin-Huxley model rather than physiological realities (except possibly for the sodium channel inactivation *h*-gate), but they are very widely used in computational neuroscience, so they are worth examining (Figure 4).

In the resting afferent, before any stimulation, the sodium inactivation open probability (*h*) is about 0.6, indicating that in this model about 40% of sodium channels are normally inactivated even at rest. However, when closing the spinal gate through pre-synaptic inhibition mediated by a dIPSP, the early subthreshold depolarization reduces the *h*-value even further, before the spike itself is generated (Figure 4b). This increases the number of sodium channels that are *pre*-inactivated, and therefore unavailable to open during the spike. The amplitude and duration of the sodium conductance during the spike is therefore reduced, and so consequently is the amplitude and duration of the spike itself. In contrast, a hyperpolarizing IPSP *increases* the *h*-value, thus reducing pre-inactivation (Figure 4c). This allows an even greater peak sodium conductance than without any inhibition at all, and thus partially counteracts the shunting effect produced by the increased chloride conductance.

The sodium channel activation variable (*m*) increases during the dIPSP, but the *m* value remains quite low. In the HH model there are 3 *m* gates but only one *h* gate. This means that overall sodium channel conductance is proportional to m^3h, so the small increase in *m* cannot compensate for the decrease in *h*.

The potassium activation open probability (*n*) also increases during the dIPSP, producing an increase in potassium conductance before the spike. In the

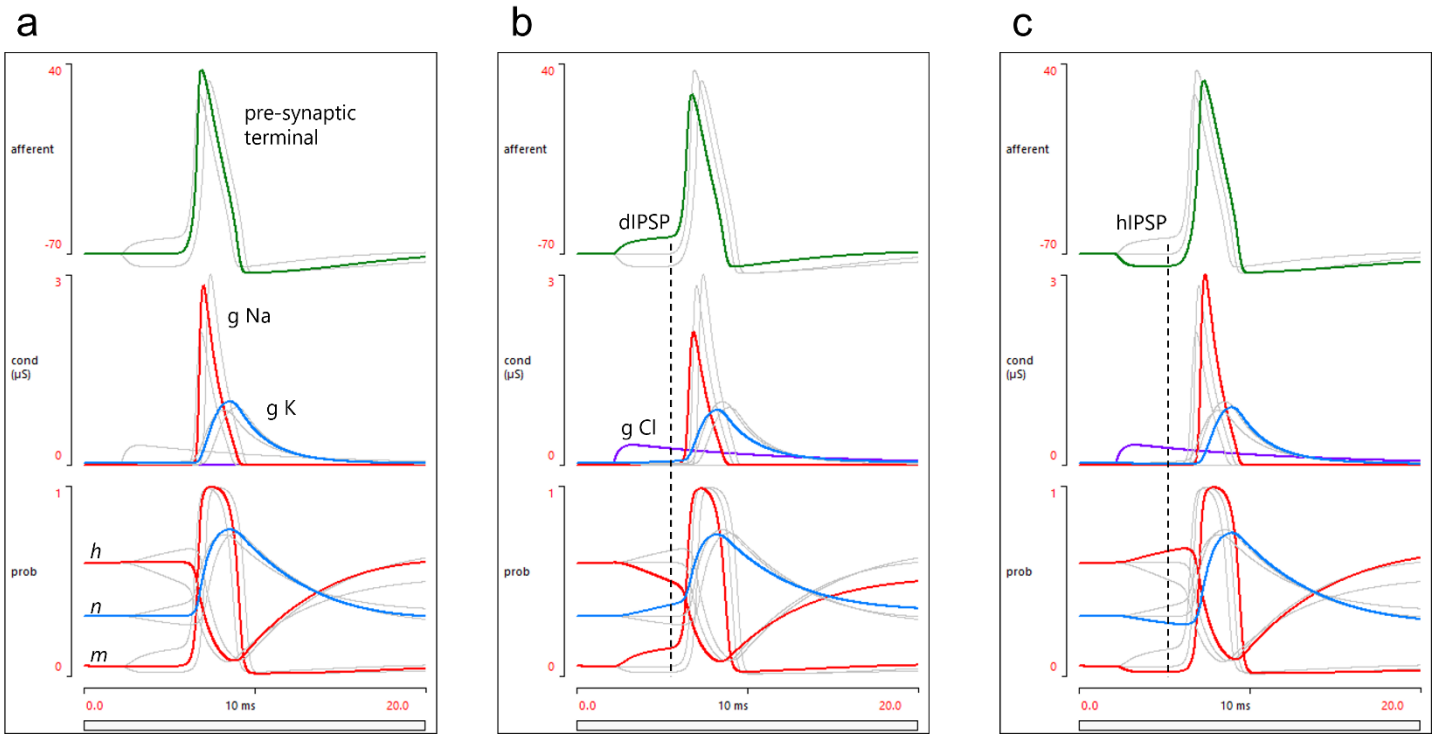

Figure 4. The effect of the polarity of pre-synaptic inhibition on the activation and inactivation gate variables of the sodium and potassium channels. Each panel shows the same 3 superimposed sweeps, but the sweeps are highlighted in turn, with the non-highlighted sweeps shown in grey for comparison. All data derive from the afferent central terminal compartment. *a.* Control with no pre-synaptic inhibition. *b.* Inhibition mediated by a depolarizing IPSP. *c.* Inhibition mediated by a hyperpolarizing IPSP. Top axis: The membrane potential (green). Second axis: The sodium (red), potassium (blue) and chloride (magenta) conductances. Bottom axis: The *m* (activation) and *h* (inactivation) gate variable of sodium channels (red), and the *n* (activation) gate variable of the potassium channels (blue). The dashed vertical lines in b and c show the timing of the IPSP preceding the afferent terminal spike.

HH model, however, potassium conductance varies with the 4th power of *n*, so the conductance increase is very small, and does not contribute much to the decrease in spike amplitude. Furthermore, the potassium conductance during the falling phase of the spike is actually reduced by activating the dIPSP (presumably because of the reduced spike peak amplitude), so it does not contribute to the reduced duration of the spike – that must be due to the reduced sodium channel conductance itself.

Caveat

At this point it may be worth reminding students that when we use simulation to dissect the mechanism of pre-synaptic inhibition, we are studying the *model* that we constructed, not a real system. The model is evidence-based in its overall functionality, but specific numerical parameters are largely derived heuristically. The conclusion from the present simulation is that inactivation of sodium channels in the pre-synaptic terminal is a major contributor to pre-synaptic inhibition. This conforms with earlier research-level simulations and physiological studies (e.g., d'Incamps *et al*., 1998, Zhang and Jackson, 1995), and provides a plausible explanation for why in real systems such inhibition involves *depolarizing* IPSPs. However, by adjusting model parameters such as the strength of the conductance changes, the anatomical location of the inhibitory input, and the properties of the voltage-dependent channels, models in which *shunting* is the major contributor to inhibition can be generated. Indeed, in some systems showing PAD there is physiological evidence that sodium channel inactivation plays little if any part in the inhibition, and models can be built that have that characteristic (Cattaert et al., 2001). In such systems one would have to look for alternative explanations for the depolarizing nature of the inhibition.

Gate Control of Pain

The simple model of pre-synaptic inhibition described above can be elaborated by incorporating it into a circuit representing the gate control of pain (Figure 5).

In this circuit, the ascending interneuron transmitting the pain sensation to the brain is modelled as a spiking compartmental axon. Also, there is an additional afferent path representing mechanosensory input such as that produced by touch (rubbing) applied in the same region as the pain stimulus, and this afferent also activates an ascending interneuron to transmit the sensation to the brain. This non-nociceptive afferent, however, is now also the element that activates the pre-synaptic inhibitor, i.e., it closes the gate in the pain pathway.

If the pain receptor alone is stimulated, the nociceptive afferent excites the ascending pain pathway and the unfortunate victim experiences the pain as a conscious

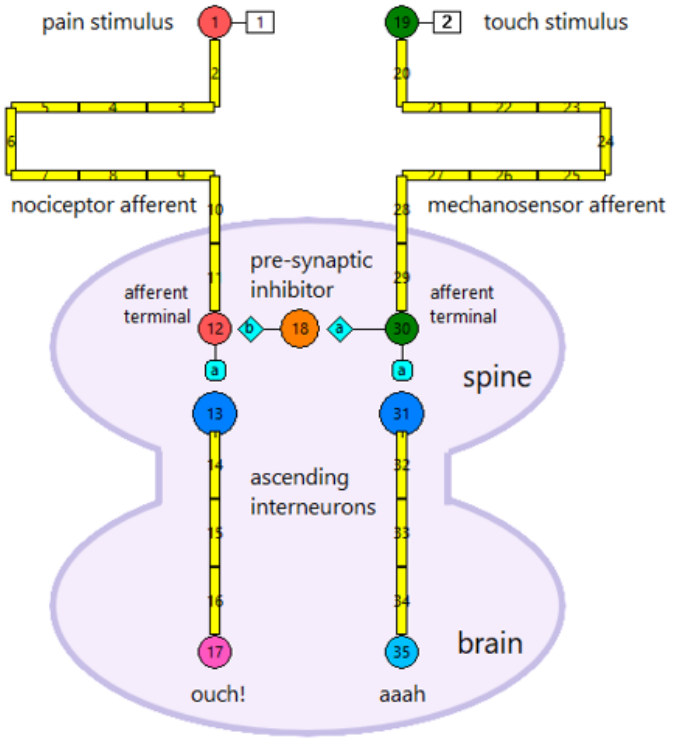

Figure 5. A circuit simulating the gate control of pain by non-nociceptive (touch) afferent stimulation. The pre-synaptic inhibition circuit in Figure 1 is extended by adding a spiking axon to the ascending interneuron conveying nociceptive information to the brain (13-17). The pre-synaptic inhibitor is now synaptically stimulated by a non-nociceptive mechanosensory afferent (19-30), which also synaptically stimulates an ascending interneuron that conveys touch information to the brain (31-35).

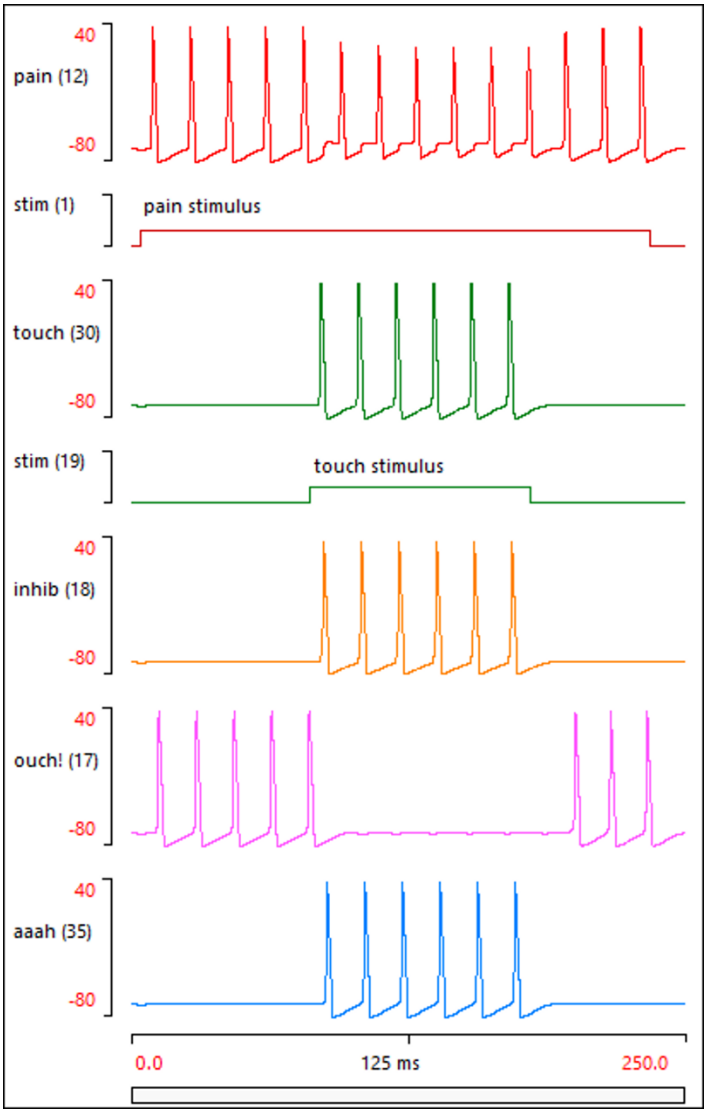

Figure 6. The gate control of pain in operation. A painful stimulus activates a nociceptive afferent (red traces; 1,12), and initially this activates an ascending interneuron that conveys the pain signal to the brain (magenta trace; 17). After a short interval, a touch stimulus is applied that activates a non-nociceptive mechanosensory afferent (green traces; 19, 30). This activates both an ascending interneuron that conveys the touch sensation to the brain (blue trace; 35), and a local inhibitory interneuron (orange trace; 18) that pre-synaptically inhibits the nociceptor central output terminal (12), interrupting the flow of the pain sensation to the brain for the duration of the touch. The trace numbers are shown in the axis labels and refer to the neurons/compartments in the simulation circuit (Figure 5).

sensation (the ouch! output, Figure 6). If, however, the mechanosensory receptor is stimulated during ongoing pain, the pre-synaptic inhibitor is activated (along with the ascending touch interneuron), and pre-synaptic inhibition closes the pain gate. The pain signal no longer reaches the brain, although the touch sensation does (the aaah output, Figures. 5, 6). When the touch stimulus ceases, the pain sensation returns.

Dorsal Root Reflex

When a depolarizing potential is delivered to a spiking neuron there is the evident possibility that the neuron might spike as a result. In normal PAD this does not occur because the depolarization is below threshold (Fig 2c, 7a), but, under certain pathological conditions, disturbance of the chloride homeostatic mechanism may cause the intracellular chloride concentration in afferents, including nociceptors, to rise to levels that take its equilibrium potential *above* spike threshold. This can trigger a “dorsal root reflex” (DRR), in which stimulation of non-nociceptive afferents elicits spikes in nociceptors originating in their central terminals and propagating antidromically to the periphery (Figure 7b). At first sight, the generation of nociceptive spikes in response to PAD would seem to obviate the gate control of pain. In the simulation, however, the PAD-generated central spikes are reduced in amplitude just like orthodromic spikes impinging on normal PAD, and consequently they too release less transmitter than an orthodromic spike not pre-synaptically inhibited by PAD. This was also found in more detailed simulations backed up by dynamic clamp experimental data conducted on acutely dissociated somata from dorsal root ganglia (Takkala et al., 2016). As the nociceptive spikes propagate peripherally, however, they escape the influence of the PAD and recover in amplitude (Figure 7b, top axis). (So far as I know, this latter phenomenon has not been commented on in previous

reports.)

What are the consequences of the DRR? One possibility is that it enhances pain reduction by blocking some orthodromic nociceptor spikes by collision. The probability of this occurring is quite low, however, given the relatively long inter-spike interval of both types of spikes compared to the conduction delay in the afferent path. Another possibility concerns the peripheral effects of the spikes. Nociceptors release various vasoactive peptides at their peripheral receptor sites, and these can accentuate the inflammatory response of peripheral tissue to injury (neurogenic inflammation; Lin et al., 1999), which in turn can increase the sensitivity of nociceptors, exacerbating the pain sensation, or even producing allodynia. Whether the DRR is therefore an adaptive response leading to increased activation of the immune system and increased guarding of damaged tissue, or an unfortunate side-effect of the gate control mechanism resulting in even greater pain, is still an open question.

DISCUSSION

"All models are wrong, but some are useful" is an aphorism whose underlying concept is usually attributed to the statistician George Box (e.g., Box, 1976). The numerous simplifications built into the models presented here mean that they certainly conform to the first part of that phrase. However, perhaps paradoxically, it is these simplifications that hopefully make the second part true as well. The models are intended as an aid for teaching and understanding rather than to test or verify a specific physiological hypothesis. Given this aim, attempts to produce more elaborate models would, in my opinion, be counter-productive because they would risk burying the user in detail that was not essential to their understanding of the core concepts (and because much of that detail would essentially be little more than informed guesses).

Nevertheless, it is important to be aware of key limitations to the models, and perhaps the most important is this. The spinal gate mechanism mediated by $GABA_A$-receptor

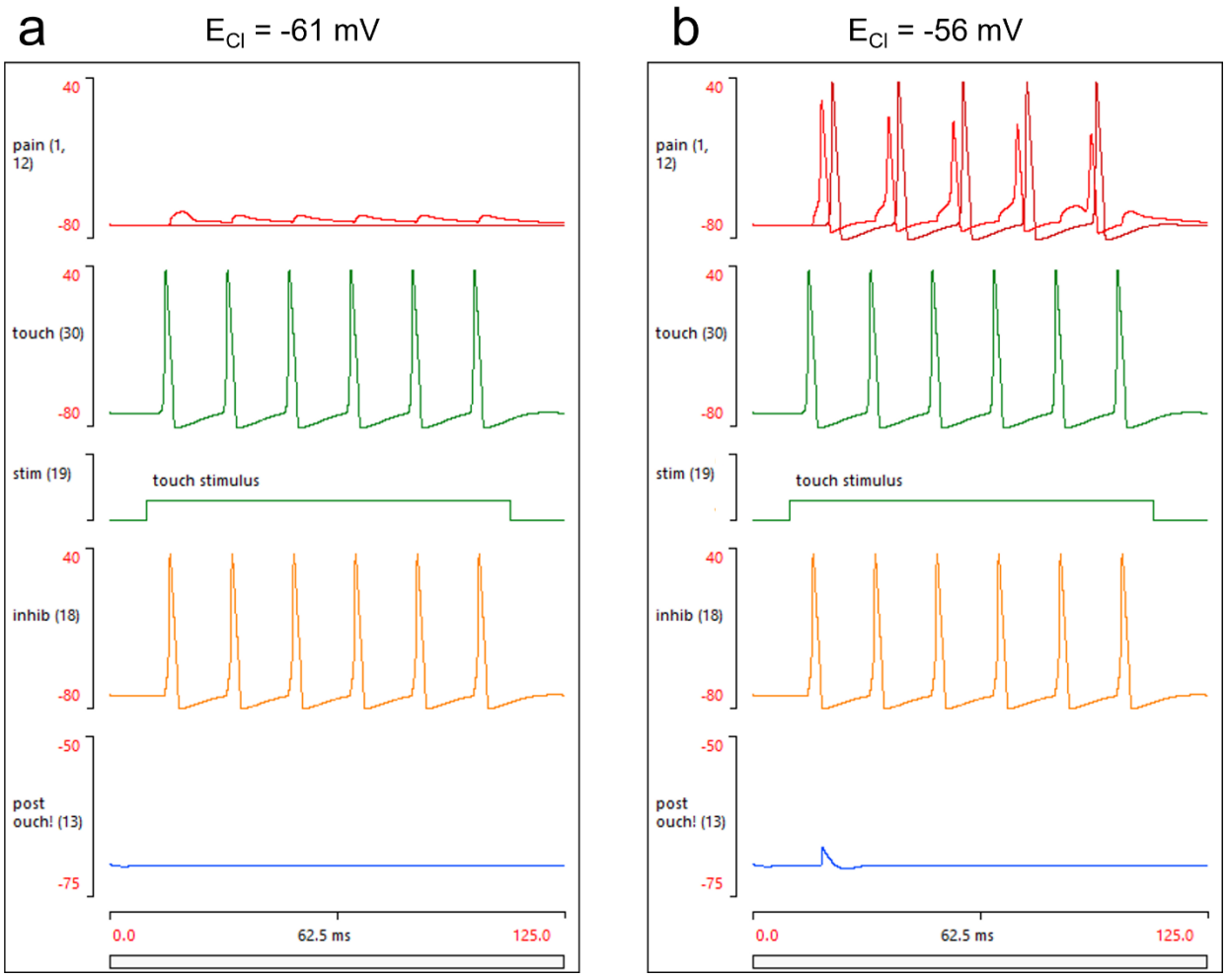

Figure 7. The dorsal root reflex. *a.* Normally, the equilibrium potential of chloride (-61 mV in these simulations) is below threshold in the afferent terminal, and touch-elicited PAD does not elicit spikes in the nociceptive afferent. *b.* The chloride equilibrium potential (-56 mV) is above threshold and PAD now elicits antidromic spikes in the afferent. Top axis, red: nociceptive afferent recorded centrally (12) and peripherally (1). Second axis, green: touch afferent recorded centrally (30). Third axis, green: touch stimulus delivered peripherally (10). Fourth axis: inhibitory interneuron (18). Bottom axis: ascending nociceptive interneuron recorded at spinal input (13). (The trace numbers are shown in the axis labels and refer to the neurons/compartments in the simulation circuit (Figure 5).

induced pre-synaptic inhibition is just one of many mechanisms that operate in parallel. Nociceptor pre-synaptic terminals have many other types of receptors, including $GABA_B$, NMDA and various opioid receptors, and modulation almost certainly occurs at spinal post-synaptic as well as pre-synaptic sites. Furthermore, pain modulation can occur at many supra-spinal locations, and pain itself is a multi-dimensional experience - Melzack and Wall (1965) wrote that "the concept of a 'pain center' in the brain ... is pure fiction". One of the most fascinating aspects of that multi-dimensionality is the occasional dissociation of the *awareness* of pain (including its intensity) and the negative affect (i.e., intense dislike) that normally goes with it. This is a common effect of exogenous opioid analgesia, but also can apparently occur under hypnosis, or as the result of brain damage (pain asymbolia). However, despite these limitations, the gate control theory has been one of the most influential in the history of pain research, and it provides a satisfying explanation at the cellular level for something with which both students and teachers are familiar – that rubbing a painful area can, within limits, make it feel better. It also provides a possible scientific basis for the use of TENS (transcutaneous electrical nerve stimulation) as a non-pharmacological option for pain reduction.

Neurosim has been used for many years in teaching neuroscience at St Andrews and other universities. Personal observation of students in my own teaching indicates that the vast majority rapidly become familiar with the program interface and can thus concentrate on understanding the underlying science rather than learning how to control the program. Anecdotal evidence gathered from voluntary end-of-semester module questionnaires indicates that most students believe that simulation exercises increased their understanding of the topic in question, but I have not carried out any systematic investigation (e.g., before and after quizzes etc.) to confirm whether this is in fact the case. What I can state with certainty is that developing these simulations increased my own understanding of the topic and made me more aware of the physiological issues underlying the gate control theory of pain. It is in that spirit that I wish to make the simulations available to other teachers and students.

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