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The role of N-methyl-D-aspartate (NMDA) receptors in wind-up: A mathematical model

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We present a mathematical model for the phenomenon of wind-up (Mendell, 1966, *Exper. Neur.* **16**, 316–22) which occurs in many neurons. We concentrate on its occurrence in the substantia gelatinosa of the dorsal horns of the spinal cord, where it is connected with certain pathological and nonpathological pain states. The model is a development of the model by Britton & Skevington (1989, *J. Theor. Biol.* **137**, 91–105) for Melzack & Wall's gate control theory of pain (1965, *Science, New York*, **150**, 971–9; 1982, *The Challenge of Pain*, Penguin: Harmondsworth), modified to take account of more recent information. Its variables are the electric potentials of various cells in the midbrain and the spinal cord. Britton & Skevington's original model simulated many of the phenomena observed in acute pain in humans, but not the wind-up mechanism. This is not surprising, since this model did not include the N-methyl-D-aspartate (NMDA) receptors that are now recognized as being crucial to the phenomenon. Here we rectify this omission, and obtain good agreement between the model and experimental data on wind-up. The positive feedback that NMDA receptors exhibit is shown to be the essential feature in producing wind-up. As an independent test of the model we simulate a completely different experimental set-up, and obtain good qualitative agreement with data there. Finally, we present a prediction of the model that has yet to be tested experimentally.

Keywords: acute pain; NMDA receptors; wind-up; mathematical modelling.

1. Introduction

We begin with a brief and simplified description of the neurophysiological mechanisms which cause pain to be experienced and inhibited. For a fuller description, see, for example, [21, 27]. The skin, muscles, joints, and some of the viscera contain certain receptors attached to nerve fibres. Following [3], we shall concentrate on cutaneous sensation. We are concerned with three types of nerve fibres from the skin to the spinal cord. The first type are known as C fibres, which are unmyelinated (i.e. without a covering of a fatty sheet of myelin), and hence they conduct impulses relatively slowly, at around 0.25–1.25 m s^{-1}. The second type are known as Aδ fibres and they are thinly myelinated, conducting impulses rather more quickly at approximately 6–30 m s^{-1}. Finally, there are the Aβ fibres, which are heavily myelinated and conduct even more quickly, at around 30–100 m s^{-1}. Now C and Aδ fibres are of small diameter (0.25–1.5 and 1–5 μm, respectively) whereas the Aβ fibres are of

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large diameter (5–15 μm). The small-diameter fibres (i.e. the C and Aδ fibres) connect with the substantia gelatinosa (SG) and cells deeper in the dorsal horns, whereas the large (i.e. Aβ) fibres connect with these cells and with the dorsal column as well. Each of these fibres is attached to a receptor in the skin, which may be a Meissner's corpuscle, a Pacinian corpuscle, a Ruffini or Krause end-organ or, for the great majority (60–70%)—and the most important for the study of pain—a free nerve ending.

When the receptors are stimulated, nerve impulses travel along the nerve fibres to various systems in the spinal cord of which we shall concentrate on two. The first of these systems is the SG in the dorsal horns. The nerve cells here are small and are connected to one another by short fibres and also to other cells situated deeper in the dorsal horn. The second system is also composed of cells in the dorsal horn, both in the most superficial layer, lamina I (a thin layer of grey substance forming the dorsal-most part of the spinal grey matter), and also in deeper layers, including lamina V. These cells are stimulated directly by nerve impulses from the receptor-fibre units of the skin; there are cells in this region whose axons form part of ascending tracts which connect with lower centres in the brain and which are also an integral part of the action system designed to deal with pain. There is also feedback from the brain to the cells of the spinal cord via descending tracts. The pattern of impulses arriving at the spinal cord from the periphery and from the brain determines the firing pattern of the spinal-cord neurons, which influences the pain which is felt. This pattern is not the sole influence because the signal may undergo extensive processing in the brain. Despite this, there is often a high correlation between spinal-cord firing rates and reported pain (see, for example, [27]), and for the purposes of this paper we shall equate firing rates of the ascending-tract neurons with pain which is felt.

A neuron that is repeatedly given the same stimulus does not necessarily repeatedly give the same response—the response may decrease or increase with time. Wind-up, which was first characterized by Mendell [24], is a progressive, and sometimes sudden, increase in the response of a neuron that is repeatedly stimulated. It may be demonstrated in spinal-cord neurons when C afferent fibres are stimulated periodically at frequencies ranging from 0.2 to 2.0 Hz [35]. The average frequency of their output starts at a low level, and remains at this level for a time of the order of 10 s. The frequency then jumps to a higher level, where it remains for as long as the stimulation is continued, and for as much as several tens of seconds longer than this. The connection with pain in human subjects was demonstrated in [28]. Wind-up has recently been implicated in many nonpathological and pathological pain states, such as second pain, ischaemic pain, allodynia, hyperalgesia, causalgia, and other neuropathic pain [2, 5, 17, 18, 26, 29]; see also the reviews [6, 31]. The cells involved in this wind-up pain are dorsal-horn neurons, and we shall concentrate on these cells in this paper. The dorsal horn contains cells with a type of excitatory amino-acid receptor—the N-methyl-D-aspartate (NMDA) receptor—that potentiates post-synaptic potentials [1, 13, 32]. Normally, the NMDA ion channels are blocked by Mg^{++} ions [20] so that no excitatory compound will have any effect on the receptor. However, if the membrane becomes depolarized, the blockage disappears and Na^{+} and Ca^{++} ions can enter the cell, leading to further depolarization. This effect operates on a slow time scale compared to an action potential, and it leads to the

hypothesis that the superposition of the effects of many action potentials mediated by the NMDA receptors may have a cumulative effect over time, and thus lead to wind-up [7, 9, 10, 33, 34]. If this is so, it could have a significant impact on the search for novel approaches to the treatment of pain, since NMDA antagonists may be promising agents for the treatment of persistent pain [8, 11, 31]. Progress has been made in this direction [2, 5, 17, 18, 26, 29].

We use a mathematical model to investigate the connection between wind-up and NMDA receptors. We base our model on the circuitry suggested by Melzack & Wall in their gate control theory (GCT) for pain [22, 23], modified to take account of more recent information, as shown in Fig. 1. Every mathematical model is a simplification and an idealization and consequently a falsification [36], and one can only attempt to ensure that the salient features of the phenomenon have been retained. In this case the details of the circuitry are certainly oversimplified (cf. [37]), but the broad picture painted by the GCT is now accepted, and it is the only theory of pain explicit enough to be cast in mathematical terms. There are, without doubt, cells in the dorsal horns of the spinal cord that transmit information to the midbrain and beyond, such as the wide-dynamic-range cells of lamina V and the nociceptive specific cells of lamina I [27]. We shall refer to such cells as T cells. There are also descending pathways that inhibit this transmission [19]. There is little doubt that there are excitatory and inhibitory cells in the SG which are connected to the T cells [30]. The connection may be via interneurons, although these are not included in the model. Small afferent fibres may excite the T cells directly (raising their potential towards the threshold at which they fire) or indirectly through interneurons in the SG [30]. It may be that different (myelinated and unmyelinated) small fibres use different mechanisms, and we include both direct and indirect excitation. Large afferent fibres also excite the T cells directly or via interneurons, but they may also inhibit them through interneurons in the SG [30]. This is a controversial statement, but we shall present numerical results in this paper that, together with the experimental results in [14], provide evidence to support it.

2. The mathematical model

The main variables in the model are the electric potentials of the various cells and their firing rates. The time scale that we work on is one of a few seconds, and hence we neglect any very-short-term effects such as action potentials. The cell potentials that we work with are the *slow* potentials, or moving time averages of membrane potentials at the soma, and the firing frequency of a particular cell is assumed to be a function of its slow potential [38]. For effects on such a time scale, this is a good approximation. The slow potential is defined as

$$\bar{V}(t) = \frac{1}{s}\int_{t-s}^{t} V(\tau)\,d\tau,$$

where s is some appropriately chosen interval of time. The effect of this time averaging is to average out rapid temporal variations which take place on a time scale shorter than s, for example, action potentials. Any long-term effects such as plasticity are

neglected. As in previous work [3, 4], we shall consider inputs and outputs to one particular T cell only and assume that all the neighbouring T cells behave in a similar manner. We shall also assume, for simplicity, that each T cell is stimulated by one C and one Aβ nerve fibre from the skin (with frequencies x_s and x_l, respectively) and one inhibitory and one excitatory SG cell. Our calculations show that the inclusion of Aδ fibres or allowing more than one of any of these would not change the results. The slow potentials we shall work with are denoted by V_i, of the inhibitory SG cell, V_e, of the excitatory SG cell, V_t, of the T cell, and V_m, of the relevant area of the midbrain. The frequencies x_i, x_e, x_t, x_m at which these cells fire are therefore functions of the slow potentials:

$$x_i = f_i(V_i), \quad x_e = (V_e), \quad x_t = f_t(V_t), \quad x_m = f_m(V_m).$$

We assume that the potentials V_k depend on the frequencies of the impulses arriving at their dendrites from various sources, and on the dendrites and synaptic junctions themselves, whose properties we shall assume to be constant over the time scales that we are considering. The effect of an input frequency x_j to an excitatory or inhibitory synapse of a cell of potential V_k will be to raise it by Φ_{jk}, where [12]

$$\Phi_{jk} = \alpha_{jk} \int_{-\infty}^{t} h_{jk}(t - \tau) g_{jk}(x_j(\tau))\, d\tau. \tag{2.1}$$

The parameter α_{jk} is equal to 1 for an excitatory synapse and to -1 for an inhibitory synapse, h_{jk} is a positive, monotone decreasing function, and g_{jk} is a bounded, strictly monotone increasing function satisfying $g_{jk}(0) = 0$. We take the simplest form for h_{jk},

$$h_{jk}(t) = \frac{1}{\tau_k} \exp\left(-\frac{t}{\tau_k}\right), \tag{2.2}$$

which represents a simple *RC*-network, where τ_k is the time constant of the membrane. The total effect of all inputs on the potential of cell k gives

$$V_k = V_{k0} + \sum_j \Phi_{jk}, \tag{2.3}$$

where V_{k0} is the resting potential of the cell. This assumes that the system is linear; this is a good approximation, at least for small variations in the variables. This assumption may be relaxed without qualitatively affecting the results. Differentiating (2.3) and using (2.1) and (2.2) yields

$$\tau_k \dot{V}_k = -(V_k - V_{k0}) + \sum_j \alpha_{jk} g_{jk}(x_j), \tag{2.4}$$

where the sum is over all inputs j to the cell k. The system we study is illustrated schematically in Fig. 1 which shows the inputs from the large, x_l, and small, x_s, fibres to appropriate sites and the appropriate connections between the inhibitory (I) and excitatory (E) SG cells, the T-cell (T), and the midbrain (B). The model equations

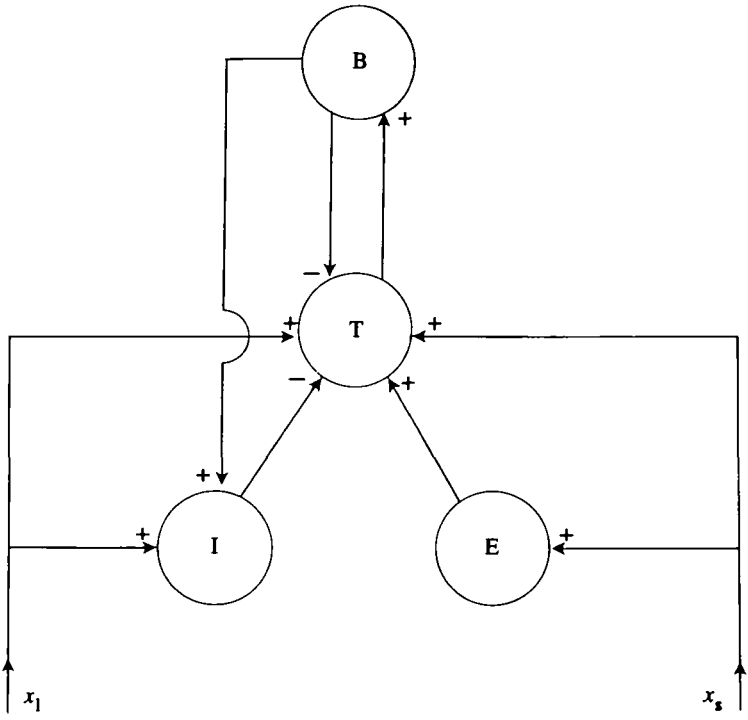

FIG 1. A schematic diagram of the circuitry for the mathematical model. The cells labelled T, I, and E are the central transmission cells and the inhibitory and excitatory neurons, respectively, all are in the dorsal horn of the spinal cord; x_l and x_s are the inputs from the large and small fibres, respectively; B represents certain important areas of the midbrain. Higher centres in the brain are also important, but they are not modelled here.

for the system are therefore

$$\tau_i \dot{V}_i = -(V_i - V_{i0}) + g_{li}(x_l) + g_{mi}(x_m), \tag{2.5}$$

$$\tau_e \dot{V}_e = -(V_e - V_{e0}) + g_{se}(x_s, V_e), \tag{2.6}$$

$$\tau_t \dot{V}_t = -(V_t - V_{t0}) + g_{st}(x_s) + g_{lt}(x_l) + g_{et}(x_e) - g_{it}(x_i) - g_{mt}(x_m), \tag{2.7}$$

$$\tau_m \dot{V}_m = -(V_m - V_{m0}) + g_{tm}(x_t). \tag{2.8}$$

It is assumed that the qualitative features of the functions f and g are known and that their parameters are in principle measurable. However, in most cases, direct measurements are unavailable and the parameters are chosen to fit the data. The explicit forms used in this paper are given in the Appendix, and the parameters involved are discussed there. The functions f give a cell's firing frequency in terms of its slow potential. We shall assume that cells do not fire until their potential reaches some threshold, and that above this threshold the firing frequency is an increasing function of the slow potential. Since the firing rate cannot increase indefinitely, the function must eventually saturate. In fact the functions f always occur composed

with a function g, and the essence is to ensure that the composition $g \circ f$ is a saturating function.

The functions g represent the effects of the inputs to a cell on its steady-state slow potential. For example, g_{1i} represents the effect of the input from the large fibres to the inhibitory cell, with similar interpretations holding for all other g_{jk}. If the input is excitatory, then increasing the input will tend to increase the slow potential, whereas if it is inhibitory it will tend to decrease it. The functions g must saturate since there is a limit beyond which no increase in the slow potential is possible. We shall usually take them to be hyperbolic tangents, since these are among the simplest increasing, saturating functions, but the functional form is not crucial. This is a good model as long as the receptors on the cell are not of the NMDA-type. However, as we have seen in the previous section, NMDA receptors do occur and they seem to be important in certain aspects of the pain system, such as in the phenomenon of wind-up. In this case, the function g is no longer simply a function of the firing frequency of the postsynaptic cells since it depends on the postsynaptic potential as well.

Non-NMDA receptors are either open, allowing depolarization of the postsynaptic or target cell, or closed, preventing such depolarization. The more the target cell is depolarized, the faster it fires. The incoming signal itself opens the receptors, so that the steady-state firing rate of the postsynaptic cell is a monotonic function of the firing rate of the presynaptic cell, that is, of the frequency of the input. It follows that it is impossible to obtain two different firing rates for the same input frequency, as occurs in wind-up experiments.

On the other hand, we know that NMDA receptors occur in (at least) three states, open, closed, and blocked [15]. Depolarization of the postsynaptic cell, via the receptor, occurs only in the open state. The open–closed transition works in the same way as in non-NMDA receptors, and it therefore depends only on the presynaptic cell, but the open–blocked transition is more complex. The blockage is caused by a magnesium ion, and it can only be removed when the postsynaptic cell becomes sufficiently depolarized. There is, therefore, a positive feedback or autocatalytic effect—input leads to depolarization, which leads to unblocking, which leads to further depolarization. We have included this effect in our model in the excitatory interneurons, because the cells with the highest number of NMDA receptors appear to be concentrated in the SG [16]. This is the reason for the dependence of V_e on g_{se} in equation (2.6). The function g_{se} must have the following properties. First, for any V_e, it is an increasing saturating function of x_s, just like the other functions g. Secondly, for any V_e we have $g_{se}(0, V_e) = 0$, since if there is no input we expect no corresponding change in the potential. Thirdly, for any $x_s > 0$, g_{se} must be an increasing saturating function of V_e, since the higher V_e is, the more NMDA receptors will be unblocked, and the more effect the input will have on the potential. We choose one of the simplest functions with these properties, by taking the saturating functions to be hyperbolic tangents.

Suitable initial conditions for the above system are imposed together with known inputs for x_s and x_1. The precise forms of all the functions f and g chosen, together with the inputs for x_s and x_1, along with the prescribed initial conditions, are given in the Appendix.

3. Results

We performed numerical simulations of the model corresponding to three experimental scenarios: the first was the effect of steady stimulation of large, cutaneous nerve fibres; the second was the effect of steady stimulation of small, cutaneous nerve fibres; and the third was the so-called ramping-off of a pain stimulus according to an experiment in [14]. The results presented below (Figs. 2–5) show the T-cell potential in each of the above scenarios, since these cells are most often used to obtain the experimental data. Qualitatively similar output to the T-cell potential is obtained for the potential in the midbrain.

There is a lot of evidence about the effect of large-fibre stimulation on pain sensation, but much of it is anecdotal. It dates back to Roman times, when Scribonius Largus recommended the use of a live electric fish, the black torpedo, to relieve the pain of gout [25]. Electric machines were used in the nineteenth century in pain relief, and transcutaneous electrical nerve stimulation (TENS) is used as a therapy today. A more familiar example is that of rubbing the skin to obtain relief after a painful knock. The ideal scientific experiment would first stimulate the small fibres alone and then, keeping this stimulation at a constant level, change the amount of large-fibre stimulation. This ideal of the independent stimulation of large and small fibres is difficult to achieve, and it has been attempted in different ways in different studies. The data are equivocal, but there is some evidence that stimulation of large fibres can relieve pain in certain circumstances (see [27] for a review of the experimental data). The model results for large-fibre stimulation are shown in Fig. 2, which clearly shows that after a small initial increase in pain, as the inhibitory

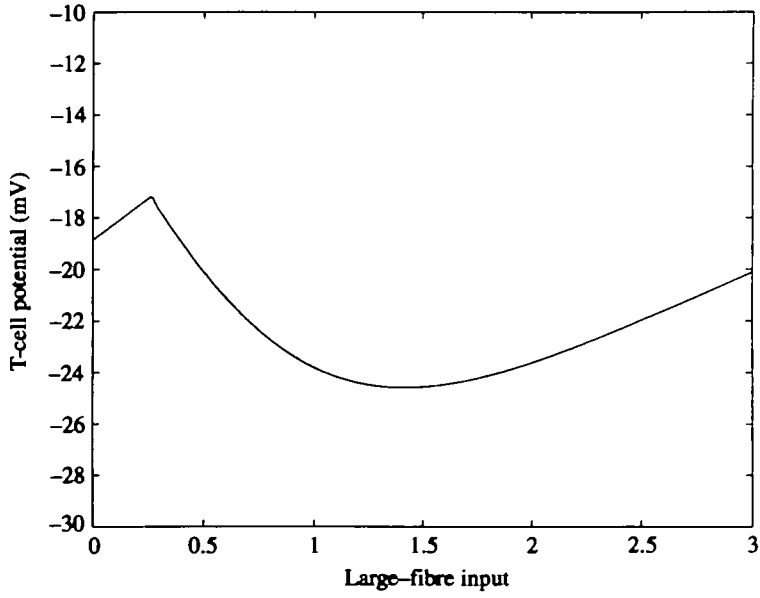

FIG. 2. The theoretical response of the T-cell potential to large-fibre stimulation, with small-fibre stimulation being held constant; $\theta_{ll} = \theta_{sc} = 0.8$.

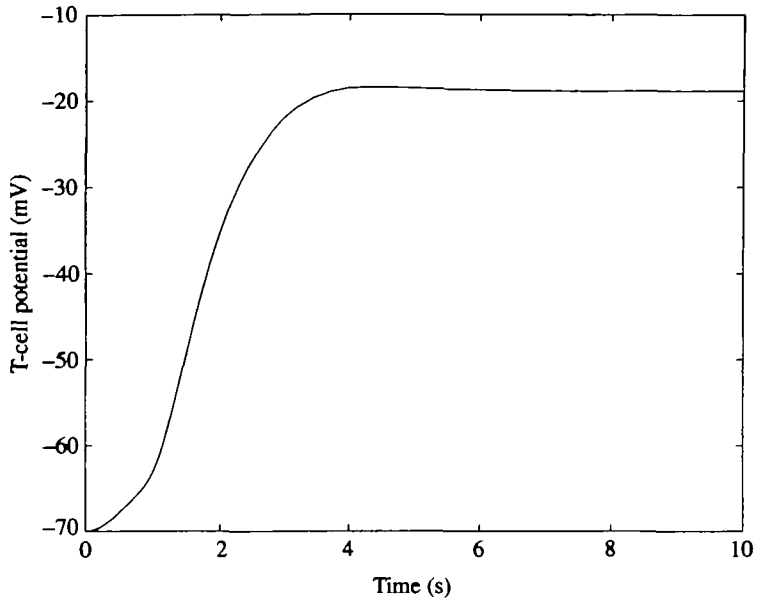

FIG. 3. The theoretical response of the T-cell potential to small-fibre stimulation alone (that is, there was no large-fibre stimulation); $\theta_{ii} = \theta_{ee} = 0.8$.

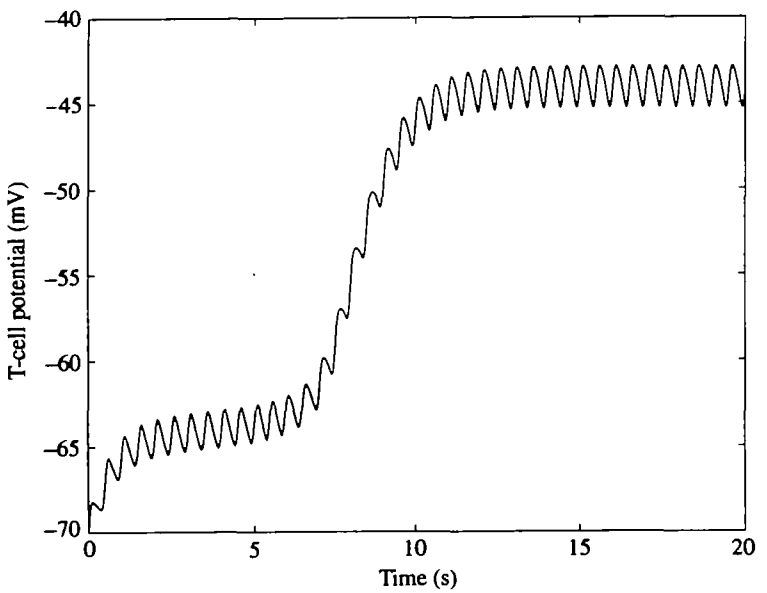

FIG. 4. The theoretical response of the T-cell potential to small-fibre stimulation at a frequency input of 2 Hz illustrating the phenomenon of wind-up; $\theta_{ii} = \theta_{ee} = 0.8$.

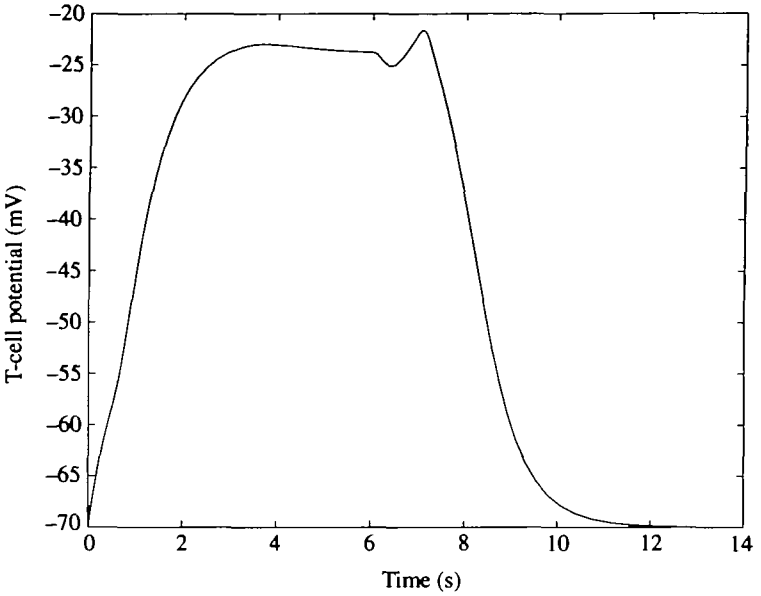

FIG 5. The theoretical response of the T-cell potential to the stimulation of small and large fibres representing the ramp-off experiment of [14]; $\theta_{II} = \theta_{\alpha} = 0.8$.

interneurons are brought up to the threshold, large-fibre stimulation does reduce pain. A further increase in stimulation is predicted to increase pain further, a result of the model which has yet to be tested experimentally. If this prediction is confirmed it would suggest that there is an optimal level of operation for TENS machines, and that stimulation above this level will increase rather than relieve pain. Parameter measurements are required to quantify this statement.

The effect for steady stimulation of small cutaneous nerve fibres, under most circumstances, is an increase in pain (or output from the T-cells) with input, at a rate slightly greater than linear (cf. [27]). Figure 3 shows that the model is in good qualitative agreement with this. An investigation of the outcome under periodic stimulation, with the frequency in the correct range, is the main goal of this paper. We carried out numerical experiments to simulate periodic stimulation at frequencies between 0.2 and 2.0 Hz. Some of the results are shown in Fig. 4, and they can be seen to be in excellent agreement with the experiments carried out on rats reported in [35]. This is a good indication that the mechanism proposed for wind-up, namely, the involvement of NMDA receptors, is correct.

As a final test for the model, we used it to simulate the result of a completely different experimental set-up. We have already seen that a constant peripheral stimulus that activates both the large and the small afferent fibres would be likely to be perceived as painful, but there would be some reduction in the intensity of the pain due to the inhibitory action of the large-fibre activity. If the peripheral stimulus was then ramped off, the large-fibre activity at the spinal level would fall away more quickly due to the different conduction velocities in the large and small fibres.

The hypothesis that large fibres have an inhibitory effect leads to the conclusion that as the pain stimulus is being ramped off there will be a transient increase in pain above that of the background level, that is, a pulse of pain. Humphries *et al.* [14] recently devised such an experiment. Potassium iontophoresis was used as an experimental pain stimulus at an upper and a lower site on a subject's dominant arm. A stimulus trial consisting of 4 s of constant pain followed by a stimulus ramp-off phase was carried out. The rate of ramp-off was varied, and the subjects were asked to indicate if they could detect a brief pulse of additional pain during this ramp-off phase; that is, this was a threshold-detection task. The results showed that the subjects were indeed clearly able to detect a pulse of pain. Figure 5 shows the model simulation of the above experiment, and once again excellent qualitative agreement can be observed, with a pulse of pain being clearly visible.

4. Conclusions

We have presented a mathematical model for the role of NMDA receptors in wind-up. The model is derived from a theory (a modified gate control theory) based on the available biological evidence, although it does not (and indeed cannot, without becoming unreasonably complex) include all that evidence. It is a testable model in that it makes concrete predictions of neuronal behaviour in certain situations. The simulations of the model show very good qualitative agreement with empirical observations of wind-up, where a periodic input at a constant frequency leads to output at a low frequency followed by a sudden increase to output at a high frequency. As in the experimental situation, the phenomenon is observed only for a small range of input frequencies. At input frequencies that are too low, the higher output frequency is never achieved, because the effect dies down too much between stimuli. At input frequencies that are too high, the higher output frequency is attained almost immediately. The mathematical model has also predicted a result which has yet to be tested experimentally concerning the stimulus of the large fibres after the small fibres have been stimulated. Anecdotal evidence of a reduction in pain for moderate levels of large-fibre stimulation is supported, but an increase in pain at higher levels of large-fibre stimulation is predicted. The model also reproduced, qualitatively, the results of an experiment by Humphries *et al.* [14]. It is interesting to note that the model does not do so unless it includes some inhibition of pain transmission by large fibres, and this work therefore lends weight to the hypothesis that such inhibition occurs. The fact that the model could simulate the results of an experiment on the ramping off of a pain stimulus, completely independently of the phenomenon of wind-up that it was designed to investigate strengthens our confidence that the model is a good one. It has passed the tests so far required of it, and we put forward in this paper a further prediction that is so far untested.

The next steps to be taken in the modelling include a more detailed analysis of the various important sites in the brain, quantification of parameters, and the inclusion of NMDA antagonists in the model in a fully quantitative way so that doses which are sufficient to prevent wind-up occurring can be predicted. Ultimately, we aim to use models of this type to begin work on modelling chronic pain, which is an altogether more complicated phenomenon.

Appendix

The precise system of equations solved numerically is given here together with initial conditions. We took all the time constants τ_k to be equal to 0.7 and assumed that all the resting potentials V_{k0} are equal to -70 mV. Equations (2.5)–(2.8) then become

$$0.7\dot{V}_i = -(V_i + 70) + 60 \tanh(\theta_{li} x_l) + 40 \tanh[f_m(V_m)],$$

$$0.7\dot{V}_e = -(V_e + 70) + 40 \tanh(\theta_{se} x_s)\{1 + 2.9 \tanh[4 f_e(V_e)]\},$$

$$0.7\dot{V}_t = -(V_t + 70) + 40 \tanh[(1 - \theta_{se}) x_s] + 40 \tanh[(1 - \theta_{li}) x_l] + 40 \tanh[f_e(V_e)] - 40 \tanh[f_i(V_i)] - 40 \tanh[f_m(V_m)],$$

$$0.7\dot{V}_m = -(V_m + 70) + 40 \tanh[f_t(V_t)],$$

where θ_{li} and θ_{se} are the proportions of the inputs that pass through the interneurons in the SG and, correspondingly, $(1 - \theta_{li})$ and $(1 - \theta_{se})$ are the proportions passing through to the T-cell. The NMDA term is the $\tanh[4 f_e(V_e)]$ term on the right-hand side of the equation for V_e.

Since the neurons we are considering usually operate far from their limiting firing rate we take as the form of the functions f to be

$$f_k(V_k) = [K(V_k - V_{thr})/(-V_{k0})] H(V_k - V_{thr}),$$

where H is the usual Heaviside function, K is a constant, and V_{thr} is the firing threshold potential, which we take in all cases to be equal to -55 mV.

For the initial conditions in each simulation, we assume that each cell is at its resting potential of -70 mV; that is, $V_i(0) = V_e(0) = V_t(0) = V_m(0) = -70$ mV.

The functional form of the inputs used for x_s and x_l depends upon the particular experiment being simulated, as detailed in the results section:

(i) constant small-fibre input, variable large-fibre input,

$$x_s = \text{constant} = 2.0, \qquad 0.0 \leqslant x_l \leqslant 3.0;$$

(ii) small-fibre input only, no large-fibre input,

$$x_s = 2 \tanh t, \qquad x_l = 0.0;$$

(ii) wind-up simulation

$$x_s = 2.5 \cos^8(2\pi t), \qquad x_l = 0.1 x_s;$$

(iv) ramp-off simulation

$$x_s = \begin{cases} 2 & \text{if } 0 \leqslant t \leqslant 7, \\ 10(7.2 - t) & \text{if } 7 < t < 7.2, \\ 0 & \text{if } t \geqslant 7.2, \end{cases}$$

$$x_l = \begin{cases} 1 & \text{if } 0 \leqslant t \leqslant 6, \\ 5(6.2 - t) & \text{if } 6 < t < 6.2, \\ 0 & \text{if } t \geqslant 6.2. \end{cases}$$

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