

# Neuromodulation of oscillatory bursting in thalamic relay neurons

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## Introduction

In August of this year, McCormick and Pape discovered and characterized a new neurotransmitter-modulated, voltage-dependent ion current that appears to be well suited to facilitate the transition from spindling to transfer mode in relay cells of the thalamus. To discuss these results requires a review of the current state of knowledge in this field.

### *Spindling and transfer mode*

The thalamus "should be viewed as a unifying entity that operates as the ultimate gatemaster and can conjure from the intrinsic properties of neurons the resting and active states of the brain" (Steriade and Llinas, 1988, pg. 650). Thus the EEG synchronized spindling of slow-wave sleep results from regularly oscillating bursts of action potentials from thalamic relay neurons, while the desynchronized EEG state of wakefulness results from linearly responsive firing of relay neurons in response to environmental input (transfer mode).

The cellular basis of these two modes was shown by Jahnsen and Llinas (1983). In a tonically hyperpolarized thalamic relay cell, a depolarizing current pulse produces a transient burst of action potentials superimposed on a low-threshold slow spike. In a slightly depolarized cell, a current pulse produces a fast train of action potentials for the duration of the pulse. The following section on oscillatory mechanisms based on this phenomenon is taken largely from the recent review by Steriade and Llinas (1988) (see also Steriade & Deschenes, 1984; Hobson and Steriade, 1986).

### *Thalamic circuits*

Thalamocortical relay neurons receive two inhibitory GABAergic inputs: from feed-forward interneurons and from projections from the nucleus reticularis (nRt) of the thalamus. All three types of neurons receive modulating inputs from nuclei in the brainstem or basal forebrain.

## Oscillatory Mechanisms

### *Ion channels*

The bursting seen in relay neurons is due to the presence of the low threshold inactivating  $\text{Ca}^{2+}$  channels described by Koystyuk et al (1988). This type of channel is inactive at rest, activates slowly at potentials below the regenerative firing threshold for  $\text{Na}^+/\text{K}^+$  action potentials, and inactivates with a time constant of about 25 ms. De-inactivation is time and voltage dependent, requiring

hyperpolarization, such that after 170 ms at -74 mV all inactivation is removed. Removal of hyperpolarization can then result in "rebound" activation of a slow, regenerative  $\text{Ca}^{2+}$  spike that triggers a short burst of  $\text{Na}^+/\text{K}^+$  spikes. Bursting is thus produced at potentials more negative than the  $\text{Na}^+/\text{K}^+$  firing threshold, by this low-threshold spike. Conversely, at the resting potential these channels are inactivated and EPSPs summate normally to produce action potentials at a rate proportional to potential.

The hyperpolarization needed to produce rebound low-threshold  $\text{Ca}^{2+}$  spikes is supplied by  $\text{Cl}^-$  currents activated by  $\text{GABA}_A$  receptors, as well as by  $I_{\text{K}(\text{Ca})}$  triggered by the  $\text{Ca}^{2+}$  influx of the spike.

Another current instrumental in the generation of spindling is the persistent, non-inactivating, voltage-dependent Na current,  $I_{\text{Na}(\text{P})}$ . This current is activated at more negative potentials than the usual inactivating  $I_{\text{Na}}$ , and it comes into play to produce a rapid removal of hyperpolarization at the end of a set period of IPSPs, which would otherwise be prolonged overlong by  $I_{\text{K}(\text{Ca})}$  and the transient inactivating potassium current (A current).

### *Synchronizing GABA input*

Synchronous bursts from thalamic relay neurons are interspersed by periods of hyperpolarization of 70 to 150 ms, producing oscillations of 7 to 14 Hz. The GABAergic nRt neurons burst continuously during this period, in phase with the relay neurons. Recently Thompson (1988) has shown that nRt input is the direct cause of relay neuron oscillations. The nRt thus acts as a general pacemaker. The synchrony and prolonged bursting of the nRt neurons themselves is presumed to involve  $I_{\text{Na}(\text{P})}$ , the  $\text{Ca}^{2+}$  spike, and intrinsic circuitry, but the precise mechanism is unknown.

## **Modulation to transfer mode**

Most of the work on neurotransmitter modulation of thalamic firing modes has been done by McCormick and colleagues (Prince and Pape) in the last three years. Just prior to their most recent finding McCormick wrote a review of these effects (1989), from which the following two subsections are drawn. I will discuss only the effects of applied agonists in vitro, but other experiments have confirmed similar effects from brainstem stimulation of nuclei supplying the corresponding neurotransmitters. All of the work with agonists has been done on the dorsal lateral geniculate nucleus and nRt of the cat in vivo.

### *Nicotinic and $M_1, M_2$ -muscarinic acetylcholine receptors*

In relay neurons acetylcholine (ACh) produces first a fast depolarization due to a nicotinic receptor-mediated direct increase of a cation conductance, followed by a slow depolarization due to an  $M_1$ -muscarinic receptor-mediated decrease in  $\text{K}^+$  conductance via second messengers. This serves to depolarize the cell away from the range where the low threshold  $\text{Ca}^{2+}$  spike operates and closer to single-spike transfer mode, as well as to increase excitability due to the decreased membrane

conductance. Synergistically, ACh has an opposite effect on the two GABAergic inputs to the relay neurons—it produces a slow hyperpolarization via an  $M_2$ -muscarinic receptor-mediated increase in  $K^+$  conductance. This produces two forms of disinhibition of the relay neurons. It inhibits the firing of the interneurons—whose feedforward inhibition would otherwise reduce excitatory sensory EPSPs—and it inhibits the burst firing of the nRt neurons, reducing the synchronous periods of hyperpolarization of the relay neurons that cause spindling.

### *Alpha<sub>1</sub>-norepinephrine receptors*

Norepinephrine (NE) produces a slow depolarization by an  $\alpha_1$ -receptor-mediated decrease in  $K^+$  conductance in both relay neurons and neurons of the nRt. The implications of this effect on the nRt neurons is not addressed by McCormick in his review or in the primary literature, however the net effect of NE on the thalamus is to inhibit oscillation and promote transfer-mode firing.

### *Serotonin and beta-adrenergic receptors -- the $I_h$ current*

Subsequent to McCormick's review, McCormick and Pape (1989) have just recently discovered a novel source of modulation of thalamic relay neuron firing mode by neurotransmitters—a hyperpolarization-activated inward current. This current shows increasing amplitude and rate of activation with hyperpolarizing voltage-clamp steps from -50 mV (time constant from 2 to 0.2 seconds), a characteristic shared by currents found in other brain regions and heart. Here serotonin (5-HT) and NE substantially enhance the amplitude and activation rate of this voltage-dependent current. Use of agonists and antagonists show that the modulation is mediated by beta receptors and by non-5-HT<sub>1A</sub>, non-5-HT<sub>2</sub> receptors. Maximum application of one neurotransmitter blocks the action of the other, indicating action on the same channels. Cyclic AMP analogs mimic the effect, and manipulation of ion concentrations show the current is carried by  $Na^+$  and  $K^+$  with a reversal potential at 0 mV.

Since the current is very small at potentials more positive than -70 mV, this source of modulation appears to be particularly well suited to counteract only the synchronized hyperpolarizing periods produced by nRt input, leaving the transfer mode unaffected. The authors tested this by observing the effect on hyperpolarizing current pulses: NA and 5-HT reversibly decreased the voltage deviation and the secondary low-threshold  $Ca^{2+}$  rebound — but they did not abolish them.

## **Discussion**

### *Mixing and matching*

Increased synaptic activity from cholinergic, noradrenergic, and serotonergic projections all serve to effect the transformation from spindling to transfer mode in thalamic relay neurons. Increase of the  $I_h$  current itself would seem to be sufficient to do this if it were stronger, but instead we find an apparent

redundancy of additional mechanisms, some inhibiting the nRt neurons, some depolarizing the relay neurons. What is the meaning of this division of labour and what are the relative contributions of each modulator? Are some of these "backup systems"? Are they there in order to regulate the nRt and individual relay nuclei separately? Is the desynchronized state of paradoxical sleep a main factor, where cholinergic inputs remain high while serotonergic and noradrenergic inputs decrease?

In particular, the time at which the increased  $I_h$  current comes into play could be investigated. If it is used to facilitate the shift to transfer mode, then it would play only a very transitory role, since the tonic depolarization due to decreased  $K^+$  conductance (from  $M_1$  and alpha receptor activation) would presumably maintain the membrane potential out of its range of action. Alternatively, increased  $I_h$  may be used to reduce refractoriness during rapid transfer-mode firing, but its slow time constant and small activation more positive than about -75 mV may argue against this. The actual membrane voltages involved in physiological arousal are not clear from the papers reviewed.

To understand the interplay of the various modulating systems, the relative effects of modulators must be assessed during natural, physiological arousal in vivo. Research to date has looked at the effects of applied agonists at non-physiological concentrations on current pulses and voltage clamp steps in in-vitro slice preparations (e.g., McCormick and Prince, 1988; McCormick and Pape, 1988). In vivo studies have used artificial stimulation of selected nuclei (in McCormick, 1989). The actual amounts of each modulating transmitter released during natural arousal need to be quantified by using, for example, electrochemistry or micro-dialysis techniques in vivo. Intracellular recordings of the corresponding responses should be made concurrently, since the amount of release does not automatically equal the intensity of response.

In conjunction, receptor binding studies could be consulted in order to take into account the proportions of receptor types being expressed by relay neurons. Receptor binding studies may prove revealing because of possible differential regulation in receptor number or affinity during changes in behavioral state or by circadian rhythms.

### *The $I_{Na(P)}$ current*

Another question is the effect on transfer mode of  $I_{Na(P)}$ . Steriade and Llinas suggest that it aids in maintaining high firing rates by opposing  $K^+$  currents during afterhyperpolarizations. Jahnsen and Llinas (1983) showed that a slight depolarization from rest activates this current to produce regeneratively a 10 mV plateau that is balanced by  $K^+$  influx for several seconds. It is not clear how this effect interacts with the depolarizations of ACh and NE and with maintaining a linear output of spikes in proportion to summated post-synaptic potentials.

### *"Innate" oscillations*

Steriade and Llinas discuss two additional modes of supposedly innate oscillatory modes of relay neurons: a 10-Hz one seen upon slight depolarization and involving  $I_{Na(P)}$  spikes; and a 6-Hz one seen upon hyperpolarization, involving  $Ca^{2+}$  spikes, and supposedly being the "substrate" for the nRt extrinsic synchronization (7-14 Hz). These were omitted from the section on oscillatory mechanisms because the explanations given are incomplete and inconsistent. It is not clear whether these "intrinsic" rhythms require continual phasic inputs in addition to tonic ones, why these rhythms are not seen when nRt input is cut, or how they can be synchronized (since according to Jahnsen and Llinas [1983] they are the basis of alpha and theta EEGs). It is not clear from the literature whether these phenomena and their relationship to spindling are actually understood. Indeed, it seems there are a lot of questions here.

## References

- JAHNSEN, H. & LLINAS, R. 1983. Electrophysiological properties of guinea-pig thalamic neurones: an in vitro study. *J.Physiol.* 349, 205-266.
- HOBSON, J.A. & STERIADE, M. 1986. Chapter 14, Neuronal basis of behavioral state control. *Handbook of Physiology, Section 1: The Nervous System.* Bethesda, Maryland.
- KOSTYUK, P.G., SHUBA, Y.M. & SAVCHENKO, A.N. 1988. Three types of calcium channels in the membrane of mouse sensory neurons. *Pflugers Arch.* 411, 661-669.
- McCORMICK, D.A. 1989. Cholinergic and noradrenergic modulation of thalamocortical processing. *Trends in Neurosci.* 12, 215-221.
- McCORMICK, D.A. & PAPE, H. 1988. Acetylcholine inhibits identified interneurons in the cat lateral geniculate nucleus. *Nature* 334, 246-249.
- McCORMICK, D.A. & PAPE, H. 1989. Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. *Nature* 340, 715-718.
- McCORMICK, D.A. & PRINCE, D.A. 1988. Noradrenergic modulation of firing pattern in guinea pig and cat thalamic neurons, in vitro. *Journal of Neurophysiol.* 59, 978-996.
- STERIADE, M. & DESCHENES, M. 1984. The thalamus as a neuronal oscillator. *Brain Research Reviews* 8, 1-63.
- STERIADE, M. & LLINAS, R.R. 1988. The functional states of the thalamus and the associated neuronal interplay. *Physiological Reviews* 68, 649-745.
- THOMSON, A.M. 1988. Inhibitory postsynaptic potentials evoked in thalamic neurons by stimulation of the reticularis nucleus evoke slow spikes in isolated rat brain. *Neuroscience* 25, 491-502.