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## **Malevolent lurkers no more: NMDA receptors come of age**

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## CLASSICAL PERSPECTIVES

**Malevolent lurkers no more:  
NMDA receptors come of age**Chris J. McBain<sup>2</sup> and Stephen F. Traynelis<sup>1</sup><sup>1</sup>*Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322 USA*<sup>2</sup>*Laboratory of Cellular and Synaptic Neurophysiology, National Institute of Child Health and Human Development, National Institutes of Health, Building 35, Bethesda, MD 20892 USA*

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Given the myriad of studies on glutamate receptors and synaptic transmission in recent years, it's hard to believe that little more than 20 years have elapsed since the first description of synaptic *N*-methyl-D-aspartate (NMDA) ionotropic glutamate receptors. Whereas today we readily accept the dual nature of excitatory postsynaptic currents comprised of rapidly activating and deactivating AMPA receptors together with slowly rising and decaying NMDA receptor responses, this advance in our understanding did not come easy. Rather, like many scientific discoveries that appear obvious in hindsight, this observation required a great deal of careful work by a number of thoughtful investigators over the course of ~6 years. Here we review two particularly important papers within this body of work that brought our understanding of excitatory synaptic transmission and its role in hyperexcitability to where it is today: centre stage in virtually every central synapse.

To gain perspective, we need to step back to a time when the newly discovered voltage-dependent  $Mg^{2+}$  blockade of NMDA receptors, arguably the most important feature of NMDA receptor function, was just becoming mechanistically understood. Work from two laboratories in 1984 had shown that extracellular  $Mg^{2+}$  could block responses of NMDA receptors in a voltage-dependent manner (Mayer *et al.* 1984; Nowak *et al.* 1984). This block by  $Mg^{2+}$  produced a region of negative slope conductance in the current–voltage relationship. This important observation made sense of disparate data from numerous groups showing NMDA responses,

presumed to be cation conductances, with paradoxical enhanced responses at depolarized potentials. This fundamental advance was consistent with the idea that at negative potentials  $Mg^{2+}$  plugged the channel pore, which prevented ion permeation despite channel activation by the agonist. In contrast, membrane depolarization relieved the  $Mg^{2+}$  blockade to allow ion flux, which explained the enhancement in current responses at depolarized potentials. Armed with this new working hypothesis, the stage was set to identify a physiological role for these receptors in brain tissue. Furthermore, the increased availability of the stereoselective competitive NMDA receptor antagonist, 2-amino-phosphonovaleric acid (APV, e.g. Davies *et al.* 1981), provided the opportunity to gain detailed understanding of what role the NMDA receptors played in brain function.

In 1988, Collingridge and co-workers (Collingridge *et al.* 1988) provided a compelling and convincing description of how NMDA receptors operate at excitatory synapses within the rodent CA1 hippocampus. At this time the rat hippocampal slice was emerging as an increasingly popular *in vitro* slice preparation. The ability to accurately position stimulating electrodes within the stratum radiatum to stimulate monosynaptic Schaffer collateral responses onto the CA1 principal cells was a highly desirable arrangement, making this a preparation whose popularity persists to this day. Under normal recording conditions and at resting membrane potentials, evoked synaptic NMDA receptor responses were blocked by  $Mg^{2+}$ . This block was further enhanced by the concomitant activation of hyperpolarizing synaptic inhibition. This observation confirmed that NMDA receptors had little role to play in monosynaptic excitatory synaptic transmission activated by low frequency (and low intensity) stimulation conditions. However, under voltage clamp conditions that minimized the effect of feedback inhibition, the authors were able to detect a small but discernable slow synaptic component at resting membrane potentials. Furthermore, with inhibition blocked and the cell now voltage clamped at depolarized membrane potentials, a dual component

EPSC could be recorded. Their elucidation of a dual component EPSP/C (Fig. 1A–C) showed clearly that the synaptic NMDA component had a similar latency as an APV-insensitive component, and thus was probably the result of the same neurotransmitter released at the same synapse.

In a second series of experiments, working in the nominal absence of extracellular  $Mg^{2+}$ , a clear monosynaptic, slow rising, slow decaying, APV-sensitive component of the synaptic response was revealed. This component was unquestionably mediated by activation of NMDA receptors by synaptic glutamate release. These authors (Collingridge *et al.* 1988) further showed the relationship of this current to the IPSP, demonstrating that an APV-induced enhancement of the IPSP probably reflected removal of depolarizing NMDA receptor response coincident with feedback inhibition. This work, together with that of others (e.g. Dale & Roberts, 1985; Thomson, 1986; O'Brien & Fischbach, 1986; Forsythe & Westbrook, 1988; Bekkers & Stevens, 1989, to name a few), clearly established the NMDA receptor as a main excitatory synaptic receptor capable of mediating long-duration depolarization during periods of depolarization, such as might occur during high-frequency stimuli, a paradigm that would keep this and many other labs busy for years to come.

A second, now classic paper, delineated perhaps more clearly than others the interplay between normal excitation, feedback inhibition, and aberrant epileptiform activity. In 1986, Dingledine *et al.* (Dingledine *et al.* 1986) showed that partial blockade of NMDA receptors on hippocampal CA1 pyramidal cells by APV was sufficient to reduce the amplitude of the paroxysmal discharge and attenuate spike firing that occurs in the presence of reduced inhibition. They hypothesized that under normal conditions, feedback inhibition drives the membrane potential to a hyperpolarized potential such that little or no NMDA receptor function is observed due to enhanced voltage-dependent  $Mg^{2+}$  block. With pharmacological reduction or removal of inhibition, the voltage-dependent  $Mg^{2+}$  block can be relieved by the action potential or burst firing triggered by AMPA receptor activation, which provides sufficient

depolarization to relieve  $Mg^{2+}$  block, allowing a strongly depolarizing NMDA receptor-mediated potential to underlie the prolonged epileptiform activity. This paper used now familiar tools such as the competitive antagonist APV and the voltage dependence of the depolarization underlying the burst to argue for an NMDA contribution to epileptiform bursting (Fig. 1*D* and *E*). Importantly, this paper also convincingly ruled out that APV was simply acting to alter the intrinsic excitability of pyramidal cells and strengthened the idea that APV inhibited NMDA receptors in a stereoselective fashion, further enhancing its status as the default antagonist for NMDA receptors.

Interestingly, the voltage-dependent  $Mg^{2+}$  blockade described above creates two hypothetical roles for NMDA receptors. In one role, NMDA receptors are slow synaptic receptors with the ability to contribute in a controlled fashion to plasticity when depolarization coincident with synaptic release of glutamate relieves their voltage-dependent  $Mg^{2+}$  block to

provide a postsynaptic influx of  $Ca^{2+}$ . In an alternative, more sinister role, NMDA receptors lie as 'malevolent lurkers', waiting to cause epilepsy should their strong voltage-dependent excitatory drive be unleashed by reductions in inhibition (Dingledine, 1986). Indeed, in what has now become recognized as pivotal in our understanding of hippocampal function, the balance between excitability and interneuron-mediated GABAergic inhibition holds the key to controlling excitatory synaptic transmission for hippocampal pyramidal cells. Again, a prediction arising from these classic papers defined an entire new avenue of research, one which to this day keeps many labs busy studying central synaptic transmission and the regulation of cellular and network excitability.

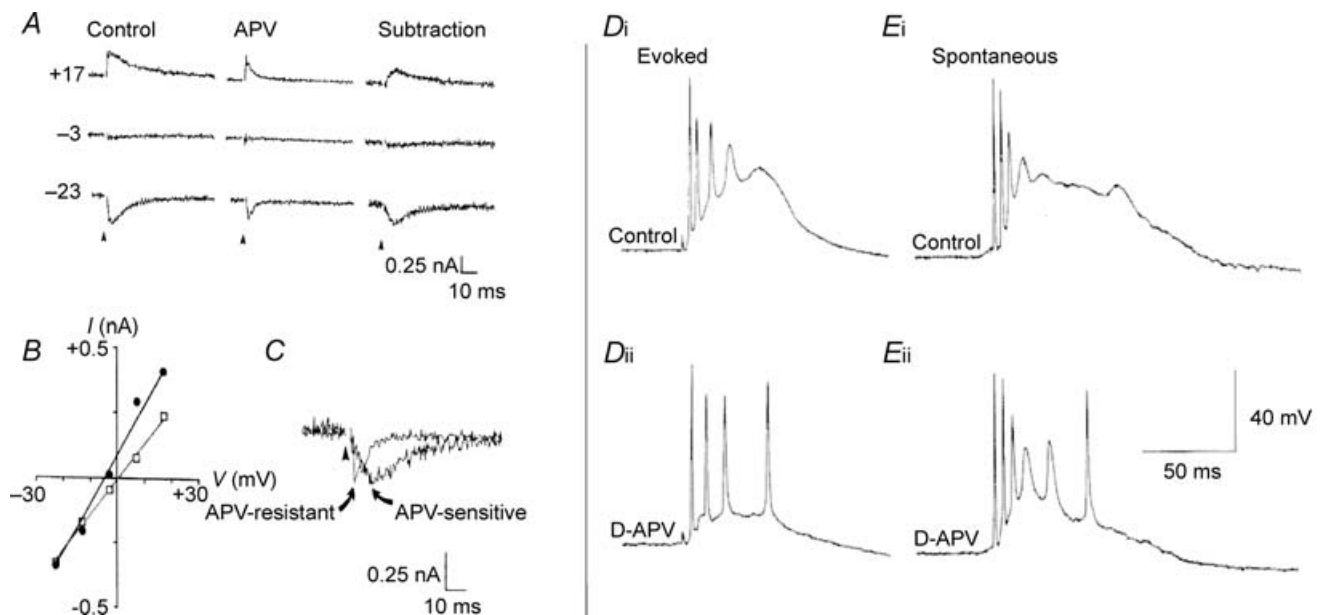
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**Figure 1. Dual-component excitatory postsynaptic currents and bursts**

*A*, averages of five successive currents recorded in the presence of 1 mM  $Mg^{2+}$  and 50  $\mu M$  picrotoxin are shown at three membrane potentials in control solution (left), 20  $\mu M$  APV (centre), and the difference between them (APV-sensitive component; right). *B*, the peak amplitudes of the APV-resistant (●) and the APV-sensitive (□) components are plotted against voltage-clamped membrane potential. Reversal potentials for the two components were  $-5$  and  $0$  mV, respectively. *C*, the APV-resistant and APV-sensitive EPSC components recorded at  $-23$  mV are superimposed to aid comparison of their time courses. Reproduced with permission from Collingridge *et al.* (1988). *D* and *E*, reduction in amplitude of the paroxysmal depolarizing shift waveform by blockade of NMDA receptors. Bursts evoked by 0.1 Hz stimulation of Schaffer-commissural path (*Di*) or occurring spontaneously (*Ei*) were recorded in the presence of 100  $\mu M$  picrotoxin. After pressure ejection of a droplet of D-APV (85  $\mu M$ ) onto the slice surface, the amplitude of the depolarization underlying both types of burst was decreased (*Dii* and *Eii*). Resting membrane potentials were  $-61$  mV (*D*) and  $-63$  mV (*E*) and input resistances were 40 M $\Omega$  (*D*) and 48 M $\Omega$  (*E*). Reproduced with permission from Dingledine *et al.* (1986).

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