Verapamil-induced changes in central conduction in patients with multiple sclerosis

ROBIN L GILMORE,* EDWARD J KASARSKIS,* RG MCALLISTER†

From the Neurology* and Research† Services Veterans Administration and University of Kentucky Medical Center, Albert B Chandler College of Medicine, Lexington, Kentucky, USA

SUMMARY The electrophysiological characteristics of demyelinated axons are sensitive to changes in plasma calcium concentration. This study investigated the effect of verapamil, a calcium antagonist drug, on brainstem auditory, visual, and somatosensory evoked potentials in multiple sclerosis patients. Eight clinically stable patients with abnormal visual and/or brainstem auditory evoked potentials and four normal volunteers were studied. During intravenous infusions of verapamil (mean plasma concentration = 130.0 ± 56.4 ng/ml), the latencies of peaks III and V were shortened ($p < 0.05$) in multiple sclerosis patients with abnormally prolonged BAEPs. The I-III ($\Delta = 0.08$ ms), III-V ($\Delta = 0.46$ ms), and I-V ($\Delta = 0.53$ ms) interpeak intervals, and the P100 latency ($\Delta = 10.15$ ms) of the visual evoked potential were similarly affected in these patients. In contrast, normal evoked potentials of both multiple sclerosis patients and control subjects were not altered compared to baseline recordings obtained 24 hours earlier. Intravenous verapamil, therefore, alters the BAEPs and VEPs of some multiple sclerosis patients with demyelinated auditory and visual pathways by shortening pathologically prolonged latencies toward normal. The present study suggests pharmacological manipulation of calcium-dependent processes, possibly at the level of the demyelinated axon, can acutely facilitate central conduction of electrical impulses in some patients with clinically stable multiple sclerosis.

The abnormal evoked potentials of patients with multiple sclerosis provide evidence for deranged electrical conduction over specific demyelinated central pathways.¹ Recent studies have suggested that fundamental changes in the electrical properties of the demyelinated axonal membrane result in the conduction abnormalities of blockade, slowing, and dispersion of action potentials.²⁻⁴ Several metabolic and physiological factors can further modify membrane excitability of demyelinated segments and presumably lead to either a clinical exacerbation or remission. Although body temperature is the best known example of such a modulating factor,⁵⁻⁷ local ionic milieu of the membrane may be of greater significance.

Experimentally-induced hypocalcaemia has been associated with transient improvement of visual function in multiple sclerosis patients with clinically stable optic nerve deficits.^{8,9} The availability and safety of calcium entry antagonist drugs, widely used

at present for treatment of cardiac arrhythmias and angina, suggested an alternative approach for investigation of the role of calcium in maintaining aberrant central conduction in multiple sclerosis.¹⁰ These agents act by influencing the transmembrane movement of calcium. It was hypothesised that the calcium antagonist drug, verapamil, might parallel the effect of systemic hypocalcaemia, transiently facilitate central conduction over demyelinated pathways, and be reflected by changes in evoked potentials.

Methods

Study subjects

Eight multiple sclerosis patients (aged 33-59 years) and four control subjects (aged 32-39 years) participated. Each patient had been symptomatic a minimum of three years and met the Shumacher criteria for the diagnosis of definite multiple sclerosis.¹¹ They were selected for: (1) severity of disability (a mean Kurtzke score of 6.4);¹² (2) absence of a clinical exacerbation during the preceding year (in order to minimise the unlikely possibility of spontaneous electrophysiological changes during the 3 day study period); and (3) abnormality of at least one of four

Address for reprint requests: Edward J Kasarskis, MD, PhD, Department of Neurology, University of Kentucky College of Medicine, Lexington, Kentucky 40536-0084, USA.

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Multimodality evoked potentials (MmEPs). All patients gave their informed consent following an explanation of the study procedures involved. None had evidence of cardiac disease nor contraindication to intravenous verapamil. All four control subjects were free of neurological disease. No individual was taking medication known to affect body temperature or multiple sclerosis (such as ACTH or steroids).

Experimental outline

Following history, general physical and neurological examination and electrocardiogram, baseline recordings of Brainstem Auditory Evoked Potential (BAEP), Visual Evoked Potential (VEP), and Somatosensory Evoked Potential (SSEP) studies were performed as described subsequently. In six of eight multiple sclerosis patients, the pre-infusion evoked potentials were unchanged from studies performed during the preceding year and attests to the apparent electrophysiological stability in the patient group. Within 24 hours, each patient received an intravenous infusion of verapamil designed to maintain constant plasma levels for at least 6 hours. Blood pressure and heart rate were monitored every 15 minutes during the first hour of infusion and, thereafter, every 30–60 minutes. Electrocardiograms were performed prior to, and during verapamil infusion. Oral temperature was recorded periodically. One hour after beginning the infusion, MmEP testing was performed exactly as on the preceding day. Special care was taken to maintain patients in an alert state during acquisition of the VEP data.¹³ If sedation was required, it was always administered after completion of the VEP study. Samples of venous blood were withdrawn for determination of plasma verapamil. In some patients, a third set of MmEP studies was performed that day after verapamil. All records were coded for later evaluation by blinded observers. Changes in evoked potential latencies were evaluated for statistical significance by using paired *t* tests.

Visual evoked potential technique

Visual evoked potentials (VEPs) were obtained using a pattern reversal checkerboard generated by a Nicolet stimulus generator. The pupils were not dilated. Continuous efforts were made to maintain the patient's level of alertness during data acquisition.¹³ Each stimulus element in the pattern subtended 22' at the eye at an average luminance of 32 cd/m². The fixation point was a 22' black target placed centrally. For patients with abnormal VEPs, a series of checks of increasing dimension was used, subtending 22', 44', 1°28', and 2°56'. The pattern reversal rate was 3.75 Hz. Scalp electrodes were placed at Oz, Fz, O1, and O2 (International 10/20 electrode placement system). The common reference electrode was at Cz, and the ground electrode at Fpz. The signal effecting the reversal of the checkerboard triggered a computer averager (Nicolet Med 80 or Pathfinder II) which received potentials differentially amplified and filtered with bandpass frequencies of 1 Hz to 1000 Hz. Two hundred and fifty six responses were averaged and replicated. In evaluating VEPs, the latency of the major positive component appearing at approximately 100 ms (P100) was measured.

Brainstem auditory evoked potential technique

The stimuli for BAEPs consisted of 75 and 90 dB HL unfiltered clicks presented monaurally to both ears at 21 Hz. Recording electrodes were placed at the vertex and both mastoids, then led into a preamplifier with a bandpass of 150 Hz to 3 KHz (–3 dB point with slope of 12 dB/octave) and amplified 100,000X. This, in turn, was processed by a computer averager (Nicolet Med 80 or Pathfinder II) with resolution 40 μ s per address and sweep time of 10–24 ms. The averager was equipped with artifact rejection based on the amplitude of the input signals. Two thousand responses were averaged and replicated at least once. Permanent records were obtained by an X–Y plotter. All latency measurements were made by identifying the positive peak of each waveform. The latencies of Jewett waves I, III and V, and the I–III, III–V and I–V Interpeak Intervals (IPIs) were quantitated.

Somatosensory evoked potential technique

Somatosensory stimuli were square wave pulses of 20 μ s duration (Nicolet 502 pulse generator), presented as a constant current at 5.1 Hz. The stimulus and trigger to the computer averager were synchronised by a pulse generator. A constant current was applied to the skin over the posterior tibial nerve at the ankle via a saddle-type bipolar stimulator with the cathode placed 3 cm proximal to the anode. Current intensity was increased to produce mild muscle contraction, or, if no twitch was produced, to at least three times the perceived sensory threshold. For recording after tibial nerve stimulation, gold plated cup electrodes were applied at the popliteal fossa (Pf), first lumbar spinous process (spL1), sixth thoracic spinous process (spT6), and seventh cervical spinous process (spC7) of the vertebral column. Scalp electrodes were placed at Cz' (2 cm behind Cz) and Fz. The spT6 electrode was used as the reference for the Pf and spL1 electrodes. Fz served as the reference for Cz' and spC7. The electrode below the knee was used as the ground. The output from each electrode was led into amplifiers with a frequency bandpass of 30 Hz to 1,500 Hz and amplification of 40,000X. Four inputs with 512 addresses per channel, a resolution of 30 to 50 μ s per address, and a total sweep time of 40 to 102 ms were used. The computer was programmed to reject any input potential exceeding 22.5 μ V. Additionally, all inputs were monitored on an oscilloscope, and computer averaging was discontinued when prominent movement artifacts appeared. One thousand to two thousand responses were averaged and replicated at least once. Data were displayed on an X–Y plotter and stored on dual floppy disks for subsequent analysis. Peaks of components were selected as previously described.^{14,15} Latencies were measured from the stimulus to the earliest positive wave in the scalp recording and to the earliest negative potential in the other recordings.

Verapamil Infusion

Each patient was administered a loading dose of verapamil (0.13 mg/kg) intravenously over three minutes, followed immediately with an infusion of 0.0038 mg/min, by a constant rate pump for 4–6 hours. Blood samples for measurement of verapamil plasma levels¹⁶ were collected at frequent intervals throughout the study period. No

Table 1 BAEPs and VEPs of multiple sclerosis and control subjects before and during verapamil infusion

Multiple sclerosis patients			VEP		BAEP: Absolute latencies						BAEP: Interpeak intervals						Verapamil (mean plasma level-ng/ml)
			OD	OS	AD			AS			AD			AS			
Subject	Age (yr)	Time	P100	P100	I	III	V	I	III	V	I-III	III-V	I-V	I-III	III-V	I-V	
1	51	B	119	112	A	A	7-80	1-72	4-42	6-92	CNC	CNC	CNC	2-70	2-50	5-20	141-0
		D	121	110	A	A	7-50	1-66	4-44	5-84	CNC	CNC	CNC	2-78	1-40	4-18	
2	36	B	A	A	1-76	A	A	1-82	A	A	CNC	CNC	CNC	CNC	CNC	CNC	75-0
		D	A	A	1-56	4-32	A	1-70	4-18	6-34	CNC	CNC	CNC	2-48	CNC	CNC	
3	51	B	146-4	157-2	A	A	A	2-34	4-36	7-86	CNC	CNC	CNC	2-02	3-50	5-52	44-1
		D	120-8	130-0	A	A	A	2-32	4-28	6-10	CNC	CNC	CNC	1-96	1-82	3-78	
4	46	B	A	A	1-74	3-92	5-60	1-38	3-76	5-66	2-18	1-68	3-86	2-38	1-90	4-28	131-1
		D	98-0*	104-0*	1-74	3-80	5-68	1-24	3-72	5-54	2-06	1-88	3-94	2-48	1-82	4-30	
5	37	B	A	A	1-64	A	A	1-68	A	A	CNC	CNC	CNC	CNC	CNC	CNC	94-9
		D	A	A	1-64	A	6-02	1-68	A	A	CNC	CNC	CNC	CNC	CNC	CNC	
6	40	B	106-0	110-0	1-48	3-86	5-92	1-42	4-04	6-14	2-38	2-06	4-44	2-62	2-10	4-72	168-0
		D	108-0	109-0	1-54	3-80	6-00	1-50	3-80	5-82	2-26	2-20	4-46	2-30	2-02	4-32	
7	33	D	A	A	1-86	4-06	6-80	1-62	4-10	A	2-20	2-74	4-94	2-48	CNC	CNC	169-0
		D	A	191-0+	1-76	3-98	6-54	1-68	3-98	A	2-22	2-56	4-78	2-30	CNC	CNC	
8	63	B	141-8	137-2	1-94	4-12	6-32	1-54	4-18	6-24	2-18	2-20	4-38	2-64	2-06	4-70	217-2
		S	140-3	137-7	1-90	4-12	6-32	1-54	4-18	6-26	2-22	2-20	4-42	2-64	2-08	4-72	
		D	132-6	138-2	1-98	4-16	6-26	1-58	4-14	6-02	2-18	2-10	4-28	2-56	1-88	4-44	
Control subjects																	
1	36	B	109-0	109-0	1-94	4-28	6-30	1-84	3-67	5-90	2-34	2-02	4-36	1-83	2-23	4-06	84-7
		D	112-1	105-0	1-90	4-18	6-36	1-64	3-61	6-14	2-28	2-20	4-46	1-97	2-53	4-50	
2	32	B	97-5	101-4	1-68	4-08	5-82	1-60	4-02	5-88	2-40	1-78	4-14	2-42	1-86	4-28	155-0
		D	98-4	104-4	1-70	4-10	5-62	1-66	3-90	5-86	2-40	1-52	3-92	2-24	1-96	4-20	
3	39	B	99-5	102-9	1-58	3-74	5-70	1-50	3-66	5-62	2-16	1-96	4-12	2-16	1-96	4-12	86-9
		D	100-6	101-1	1-66	3-74	5-78	1-50	3-66	5-78	2-08	2-04	4-12	2-16	2-12	4-28	
4	34	B	102-5	103-8	1-50	3-74	5-62	1-86	3-98	5-82	2-24	1-88	4-12	2-12	1-84	3-96	90-6
		D	98-6	104-7	1-50	3-78	5-74	1-94	4-02	5-90	2-28	1-96	4-24	2-08	1-88	3-96	

B = Before Vpm infusion, D = During Vpm infusion, A = Absent, S = During Saline infusion, IPI = Interpeak interval, CNC = Cannot calculate.
 *Stimulus subtended 2°56' visual arc, †Stimulus subtended 1°28' visual arc

patient had an adverse clinical reaction to the drug; however, as anticipated, the PR intervals were prolonged to at least 0.24 s in all subjects.¹⁷ The mean verapamil concentration was 130.0 ± 56.5 mg/ml in patients (104.3 ± 33.69 ng/ml in control subjects). This was not a significant difference.

Results

VEPs

Seven of eight patients had abnormal pretreatment VEPs. Four had bilaterally absent VEPs when tested with varying size checkerboard stimuli; three had at least one prolonged P100 latency (table 1). During verapamil infusion, the P100 latencies shortened an average of 10.15 ± 5.3 ms ($p < 0.05$) compared to pre-infusion latency (Table 2). In one patient, the P100 latency shortened as much as 27.2 ms during infusion (fig. 1A). The effect of verapamil in shortening P100 latencies could still be detected 24 hours after the infusion was discontinued. In two patients (4 and 7, not included in the statistical analysis) whose P100s were absent prior to infusion, a poorly defined P100 peak emerged when using a large check size (1°28') during infusion (fig. 1B). Moreover, in the one multiple sclerosis patient with normal VEPs prior to verapamil, no change was observed in waveform morphology or latency during infusion. This was similar to the results in normal

subjects whose VEPs were unaffected by intravenous verapamil (fig. 2). Table 1 summarises the effects of verapamil on normal and abnormal EPs.

BAEPs

Seven of eight multiple sclerosis patients had abnormal BAEPs consisting of either absent components and/or prolongation of interpeak intervals implying a prolonged central conduction time. In eight of 14 baseline studies, BAEP components were sufficiently well defined to permit calculation of interpeak intervals (IPIs). The mean interpeak intervals for the multiple sclerosis study subjects were 2.39 ± 0.11 ms, 1.97 ± 0.12 ms, 4.32 ± 0.12 ms for the I-III, III-V, and I-V IPIs respectively. These IPIs were significantly greater than the normal population in our laboratory. The latency of wave I did not change significantly with verapamil administration (table 3), however, wave III latency shortened by 0.07 ± 0.03 ms ($p < 0.01$), and wave V by 0.49 ± 0.21 ms ($p < 0.05$) during verapamil when compared to preinfusion baseline studies. The calculated IPIs also shortened during verapamil infusion; the I-III IPI by 0.08 ± 0.04 ms ($p < 0.02$); the III-V IPI by 0.46 ± 0.25 ms; and the I-V IPI by 0.53 ± 0.24 ms ($p < 0.05$). In addition, two patients (not included in the statistical analysis), developed BAEP components which were absent in the pre-

Table 2 SSEPs of multiple sclerosis patients before and during verapamil infusion

Subject	Age yr	Time	Absolute latencies							
			R Leg				L Leg			
1	51	B	N8	N22	N27	P37	N8	N22	N27	P37
		D	8.1	23.4	35.8	45.6	8.4	22.0	27.4	39.0
2	36	B	8.0	21.4	35.6	49.4	8.2	23.2	27.8	38.6
		D	9.0	28.2	A	A	9.2	A	A	A
3	51	B	8.6	28.1	A	A	9.2	A	A	A
		D	8.6	28.8	A	51.4	8.6	25.4	34.2	46.8
4	46	B	8.0	23.3	A	49.2	8.2	24.2	A	44.8
		D	9.4	23.6	A	A	9.8	26.0	32.4	A
5	37	B	9.8	23.8	A	A	10.0	25.4	A	A
		D	9.8	23.0	A	A	9.6	23.4	A	A
6	40	B	9.6	23.8	A	A	9.4	22.4	A	A
		D	ND							
7	33	B	9.4	24.0	A	A	9.3	23.0	37.2	A
		D	9.3	25.4	A	A	9.4	24.8	33.4	A
8	63	B	9.6	25.8	A	A	9.6	A	A	A
		S	9.6	23.6	A	A	9.6	A	A	A
		D	9.6	24.6	A	A	9.6	A	A	A

B = Before Vpm infusion, D = During Vpm infusion, A = Absent, S = During Saline infusion

infusion study (fig. 3). In all control subjects and one multiple sclerosis patient with normal baseline BAEPs, no changes in waveform or BAEP latency were observed.

SSEPs

All eight multiple sclerosis patients in this study had

Fig 1(A) VEPs of patient No. 3's left eye. All recordings were made from Oz-Cz. The target subtended 1°28' visual arc. Note that baseline latency of 157.2 ms has shortened 27.0 ms to 130.0 ms during verapamil infusion. Twenty-four hours later, the latency has increased but conduction is still 13.8 ms faster than baseline conduction. (B) VEPs of patient 7's left eye. The target subtended 1°28' visual arc. Both recordings were made from Oz-Cz. A VEP absent before infusion appeared during verapamil infusion.

abnormal SSEPs following tibial nerve stimulation. Of these, six had absent cortical evoked potentials and two had delayed cortical evoked potentials. Frequently, subcortical evoked potentials were neither temporally dispersed or absent. In the two multiple sclerosis patients with cortical evoked potentials, the central conduction times were abnormally prolonged. During verapamil infusion, one patient with previously absent cortical evoked potential developed a very low amplitude cortical potential, which although replicable, had complex and atypical morphology. No other significant changes in the SSEP due to acute verapamil administration could be identified (table 2). Identifying changes in the SSEP was difficult as noted by others.¹⁸

Discussion

Evoked potential measurements have gained wide acceptance in providing electrophysiological evidence of abnormal central conduction in patients clinically suspected of having multiple sclerosis. More recently, evoked potentials have been utilised

Fig 2 Visual Evoked Potential of Control No. 1's left eye.

Table 3 Effect of verapamil on evoked potentials

Visual evoked potentials	Controls*			Multiple sclerosis Patients		
	Mean difference $\pm$ SE (range)	n	p	Mean difference $\pm$ SE (range)	n [‡]	p
P100	+0.02 ms $\pm$ 0.82† (-4.0 to +3.0)	10	NS	-10.15 ms $\pm$ 5.3	6	<0.05
Brainstem Auditory Evoked Potentials						
Absolute Latency	Mean difference $\pm$ SE	n	p	Mean difference $\pm$ SE	n [‡]	p
I	+0.004 ms $\pm$ 0.03	9	NS	+0.02 ms $\pm$ 0.02	12	NS
III	-0.04 ms $\pm$ 0.02	10	NS	-0.07 ms $\pm$ 0.03	8	<0.05
V	+0.02 ms $\pm$ 0.04	10	NS	-0.49 ms $\pm$ 0.21	8	<0.05
Interpeak Intervals						
I-III	-0.04 ms $\pm$ 0.03	9	NS	-0.08 ms $\pm$ 0.04	8	<0.02
III-V	+0.01 ms $\pm$ 0.02	9	NS	-0.46 ms $\pm$ 0.25	7	NS§
I-V	+0.05 ms $\pm$ 0.04	10	NS	-0.53 ms $\pm$ 0.24	7	<0.05

*Control studies were of two types: (A) normal volunteers or (B) multiple sclerosis patients who had a single evoked potential study which was within normal limits (for example, a normal VEP and abnormal BAEP).

†- = latency or interval decreased, + = latency or interval increased.

‡This data analysis does not include the previously absent components which appeared during verapamil infusion. It includes only those data in which the component was seen in both the initial study and verapamil infusion study (so that a mean difference could be calculated).

§Significant at 0.06 level.

in order to monitor the neurophysiological status of multiple sclerosis patients during experimental therapeutic intervention. For example, Dau *et al* compared evoked potentials before and after plasmapheresis and found changes in three of seven patients,¹⁹ although the magnitude of evoked potential changes did not necessarily correlate with improved clinical status. There were several reasons why evoked potentials were chosen as an outcome measure in this experiment: (1) evoked potentials are stable over a long period of time in a given patient without a clinical exacerbation.²⁰ In this study, six of eight patients had evoked potential studies in the 14 months preceding the experiment which were unchanged when compared to the immediate pre-verapamil studies. This suggests that evoked potential changes associated with verapamil infusion are likely to be causally related and not the

result of spontaneous electrophysiological improvement. (2) evoked potentials afford an objective, non-invasive, and reproducible measure of pharmacological intervention.²¹ (3) evoked potentials appear to be sensitive to small changes in various metabolic and physical parameters. (For example, pH and temperature).⁵⁻⁷

Two types of neurophysiological changes were observed in our patients during verapamil infusion: (1) shortened BAEP and VEP latencies (see fig. 1A); (2) and emergence of new waveforms (see figs. 1B and 3). Because patients were selected for their clinical and electrophysiological stability, these changes appear to result from administration of the calcium antagonist drug rather than from transient fluctuation in central conductivity. Throughout the study, care was exercised rigorously to control body temperature, level of alertness, diet, and medication. Further support for a cause-effect relationship comes from the time course of the electrophysiological changes. In the patients who underwent post-drug study, verapamil-induced changes substantially reverted toward pretreatment values as would be anticipated following clearance of the drug from plasma (see fig. 1A). A second line of evidence stems from the fact that the electrophysiological responses were observed at plasma verapamil levels which alter intracardiac conduction through the His-Purkinje systems (prolonged P-R intervals).¹⁷

Verapamil is known to enter the central nervous system in small but measurable quantities.²² Recently, binding sites for calcium antagonist drugs in human brain have been identified.²³ Although only small concentrations are found within normal

Fig 3 BAEPs of Patient No 2. The left ear was stimulated at 90dB HL using clicks. All recordings were made from Cz to ipsilateral mastoid tip. Wave III absent before infusion appears at 4.18 ms.

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brain, it is possible that the defective blood brain barrier in areas of presumed demyelination²⁴ may allow higher CNS verapamil concentrations in patients with multiple sclerosis than in controls. The mechanism whereby verapamil alters electrical transmission in central pathways in multiple sclerosis is unknown but may reflect antagonism of calcium-dependent processes within the demyelinated axonal membrane itself. The effect of intravenous verapamil appears to affect only abnormal evoked potentials because similar concentration of the drug in controls or multiple sclerosis patients with normal evoked potentials were not associated with a generalised enhancement of central transmission. Thus, verapamil may act at the level of the demyelinated axon rather than through a more widespread mechanism such as altering calcium-dependent cellular processes required for neural transmission.

The results of this study extend the observations of Schaaf and Davis on the transient beneficial clinical effects of systemic hypocalcaemia in multiple sclerosis patients. In their clinical experiments, hypocalcaemia induced by either EDTA infusion, high dose oral phosphate, or hyperventilation, was associated with reduction in the size of scotomata and in some patients, a decrease in the frequency and amplitude of nystagmus.^{9,10} Indeed it was their original suggestion that calcium plays a critical role in modulating electrical conduction over demyelinated axons⁹⁻¹⁰ that stimulated the present study.

It is well established that verapamil inhibits transmembrane flux of calcium in virtually all tissues studied to date. Conceivably, verapamil could modify the ionic flux of calcium through demyelinated axonal membrane, and alter local electrical fields. This would have an effect on the sodium channel voltage sensors to alter the rate of sodium inactivation similar to subthreshold depolarization.^{1,10} Alternatively, verapamil could modify calcium-dependent, voltage sensitive potassium channels.^{9,25-28} There is evidence to suggest that potassium conductance is increased in areas of demyelination compared to the normal axon.^{29,30} An agent which blocks potassium channels directly would therefore be expected to improve the conduction block of demyelinated fibres.³¹ However, a drug such as verapamil which may produce an indirect effect on potassium channels would be expected to have smaller effect on the evoked potentials in normals and multiple sclerosis patients without demyelinated evoked potential pathways since potassium conductance makes comparatively less contribution during normal saltatory conduction.³⁰ This conjecture is supported by the data showing significant change in conduction times only in

patients with pathologically prolonged latencies.

Obviously, verapamil need not act on the transmembrane calcium flux at all. Recently it has been suggested that during depolarisation, activation of calcium-dependent potassium current is related to the intracellular concentration of free ionic calcium and not to transmembrane movement of calcium.³² Verapamil may affect conduction by blocking the uptake of intracellular calcium into mitochondria. This may lead to increased cytoplasmic ionic calcium, and secondarily may result in altered potassium conductance and consequent local electrical field charges. Further study of verapamil on the neurophysiology in experimental demyelination is needed to clarify these issues.

This study, in conjunction with the investigation of Davis and colleagues, emphasises the potential for pharmacological agents to modify the electrophysiological responsiveness of multiple sclerosis patients. Little is known about local factors which contribute to disorganised axonal conduction in areas of demyelination, although on the basis of these studies, calcium appears to be involved. Further investigation of the ionic milieu of the plaque may afford better understanding of the underlying neurophysiologic mechanisms.

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