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The effect of mebudipine and dibudipine, two new Ca^{2+} channel blockers, in comparison with nifedipine on Ca^{2+} spikes of F_1 neuronal soma membrane in *Helix aspersa*

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Mebudipine and dibudipine are two new dihydropyridine (DHP) Ca^{2+} channel blockers that have been synthesized by Mahmoudian et al. (1997). In previous studies, they showed considerable relaxant effect on vascular and ileal smooth muscles. These two compounds also reduced the contraction force of rat left atrium (20, 22). In the present study, we attempted to compare the inhibitory actions of these new DHPs and nifedipine on the high threshold Ca^{2+} spikes of F_1 neuronal soma membrane in the sub-esophageal ganglia of *Helix aspersa*, using current-clamp method.

At a concentration of 1 μM, two new DHP compounds (mebudipine and dibudipine) were tested for their L-type Ca^{2+} channel blocker activity. Both compounds reversibly reduced the peak amplitude of action potential and after hyperpolarization potential and markedly decreased the duration of Ca^{2+} spikes. The most potent of these DHPs was mebudipine. Neither the two new DHPs nor nifedipine changed the resting membrane potential in a statistically significant way.

Keywords: mebudipine, dibudipine, dihydropyridine antagonist, *Helix aspersa*

Selective antagonists have proven to be essential tools for characterizing functional diversity of voltage gated calcium channels in neurons (7, 26). One widely used class of compound is 1,4-dihydropyridines (DHPs) which are routinely used at μM concentrations to identify the presence of the L-type class of Ca^{2+} channels. The use of DHPs to identify the presence of L-type calcium channels usually assumes that they do not act at non-L-type channels (1, 3, 5). Mebudipine [(±)-t-butyl, methyl-1,4-dihydro-

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2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyrine dicarboxylate] and dibudipine [(±)-bis-t-buthyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylate] are two new Ca^{2+} channel blockers with 1,4-dihydro pyridine structure that were first synthesized by Mahmoudian et al. (20). Previous studies have demonstrated that they show considerable relaxant effect on vascular and ileal smooth muscle (20). They also reduce the contraction force of rat atrium and lower rat blood pressure (22). In the present study, we attempted to compare the inhibitory effects of these two new DHP derivatives and nifedipine on Ca^{2+} spikes of F_1 neuronal soma membrane in the sub-esophageal ganglia of *Helix aspersa*, using a conventional two electrode current-clamp technique.

Materials and Methods

Animals and dissection

Experiments were performed on the somata of isolated F_1 neurons of the sub-esophageal ganglia of *Helix aspersa* (Iranian garden snail). Specimens were collected from Babol, north of Iran, and ranged in weight from 4 to 7 g. For dissection, the animal was pinned onto a cork board in an extended position. The ganglionic mass with its main peripheral nerves and aorta was dissected out and then pinned by the nerves and the edges of the connective tissue into a Sylgard-grounded recording chamber (Dow Corning, Midland, MI). The overlying layers of connective tissue covering the ganglia were gently torn using two pairs of fine forceps without any pretreatment with proteolytic enzymes. F_1 neurons were visually identified by their size and colour within the right parietal ganglion of *Helix aspersa* (16).

Solution and drugs

The normal Ringer contained (in mM): NaCl, 80; $CaCl_2$, 10; KCl, 4; $MgCl_2$, 5; glucose, 10; 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES), 5; as described by Taylor (30).

The solution used for detection of Ca^{2+} spike contained (in mM): tetraethyl ammonium chloride (TEA, Sigma), 84; $CaCl_2$, 10; KCl, 4; $MgCl_2$, 5; glucose, 10; HEPES, 5. For all experiments, 4-aminopyridine (4-AP, 5 mM) which is generally accepted as a fast outward K^+ channel blocker, was applied extracellulary. Therefore, action potentials recorded in this study mainly resulted from activities of Ca^{2+} channel currents. Nifedipine, mebudipine and dibudipine were dissolved in absolute ethanol at a final concentration of 1 μM (the final concentration of vehicle in the perfusion solutions was 0.3% (v/v). The same concentration of vehicle had no effect on Ca^{2+} spikes (14, 18). The drugs were added to the perfusing Ringer solutions. The pH of solutions was adjusted to 7.8 with either Trizma hydrochloride or Trizma base (Sigma). Each solution was superfused into the experimental chamber at a rate of approximately 3.5 ml/min.

Recording technique and equipment

Intracellular recording of F_1 neurons was performed by micropipettes prepared using a micropipette puller (Stoelting, UK). Microelectrodes were filled with 3 M KCl and had a tip resistance of 1–6 MΩ. They were routinely coated with sylgard. An Axoclamp 2B amplifier (Axon Instruments, Inc, Burlingame, USA) was used in an active bridge mode. Then, data were transferred to an IBM compatible computer by means of an A/D and D/A converter (Scientific Labmaster, USA).

Parameters to measure the characteristics of Ca^{2+} action potential were amplitude (mV), duration (mSec) of action potential and the peak amplitude of after-hyperpolarization (AHP) between spikes.

The following criteria were used to measure the parameters. The amplitude of action potential was measured as the difference between the point of spike initiation and its peak amplitude. The duration of action potential was measured at half peak amplitude and the amplitude of AHP between spikes was measured from the resting membrane potential level to the peak of AHP.

In order to determine half-maximal reduction (IC_{50}) in evoked calcium spike duration based on concentration-response curve, 1 nA depolarizing current (500 mS) was injected into F1 cells under the current clamp condition in the presence of different concentrations (10^{-7} to 10^{-5} M) of mebudipine, nifedipine or dibudipine. Logistic regression analysis was performed with two parameters: slope and IC_{50}. SPSS NLR procedure was used to fit each equation and they were forced to parallel dose response curves. IC_{50} and symptotic standard errors were reported after making the fits parallel to each other.

Statistical analysis

Paired *t*-test and one way repeated measures of analysis of variance (ANOVA) were used to compare the parameters before and after the drugs application followed by the least significant difference (LSD) test. All values are presented as means ±S.E.M. and statistical significance was indicated by p values less than 0.05.

Results

In this study, three groups of experiments are reported: (i) Applying DHPs compounds extracellulary to investigate their effects on characteristics of Ca^{2+} spike. (ii) To elucidate the reversibility of the effects of applied DHPs. (iii) Adding these DHPs to the normal Ringer to examine the effect of the applied drugs on configuration of fast Na^+ action potential.

Experiments were conducted in 35 F_1 neurons of the right parietal ganglion of *Helix aspersa*. To characterize Ca^{2+} spikes in soma membrane of F_1 neurons, recording was performed after blocking voltage activated outward K^+ currents (TEA and 4-AP were added to the bathing solution) and voltage activated Na^+ inward currents (Na^+ ions

were replaced on an equimolar basis by TEA). Under these conditions, a type of Ca^{2+} spike with a plateau was spontaneously recorded from a resting potential of –35.73±5.38 mV (n=35). These spikes showed large amplitude with a plateau phase compared to the fast Na^{+} action potential in normal Ringer (75.8±11.9 versus 70.6±4.3 mV). A typical result is shown in Figure 1. Since their threshold was near –30±3.2 mV, they could be referred to as high threshold Ca^{2+} spikes (28, 31). When the DHP compounds were separately applied to the Ca^{2+}selective saline, neither agent produced significant changes in the resting membrane potential. However, the most common characteristic affected by these new DHP compounds and nifedipine in F_1 neurons was reduction of the duration and alternation of the Ca^{2+} action potential configuration. Figure 2 shows the effects of 1 μM nifedipine, mebudipine or dibudipine on the duration of Ca^{2+} spikes. Following the addition of these agents, duration of Ca^{2+} spikes was reduced significantly within 3 min. (Figs 2 and 3A, paired *t*-test: $p<0.01$).

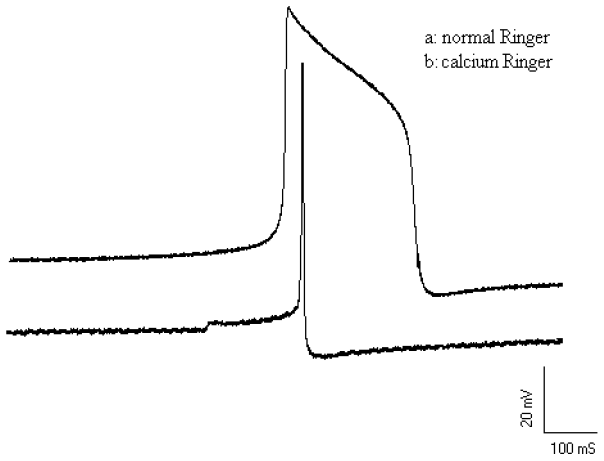

Fig. 1. The spontaneous somatic high threshold Ca^{2+} spike. Two individual action potentials recorded in normal Ringer (a) and in Ca^{2+} Ringer (b). A noticeable broadening of action potential occurred in the presence of Ca^{2+} Ringer (80 mM TEA was substituted for Na^{+} and 5 mM 4-AP was applied to the bathing media) as well as a remarkable decrease in the after-hyperpolarization peak (AHP)

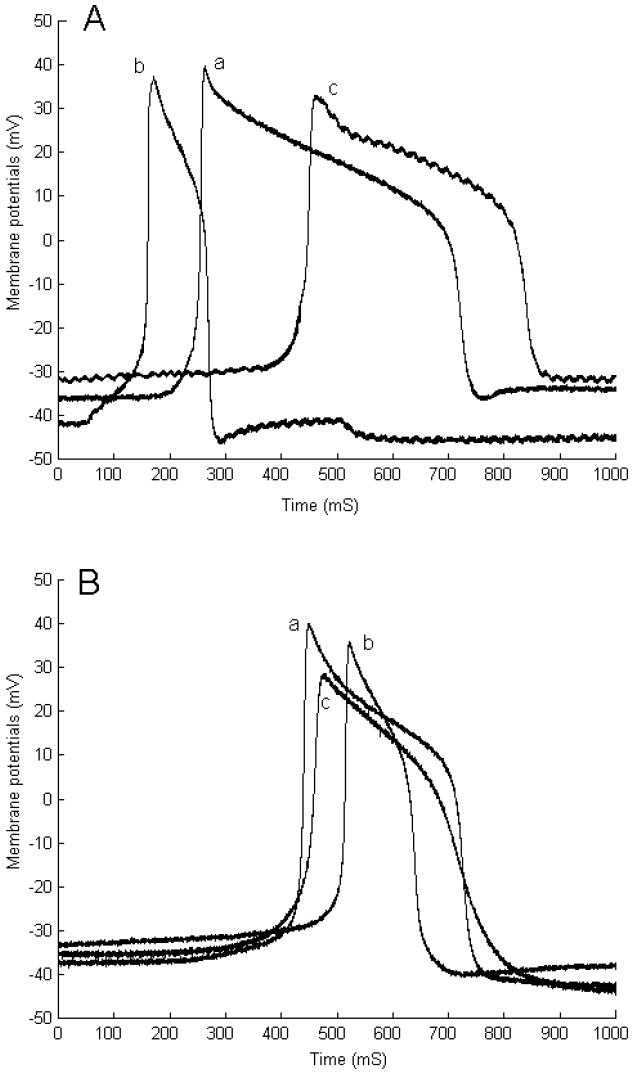
A
B
a
b
c
Membrane potentials (mV)
Time (mS)
50
40
30
20
10
0
-10
-20
-30
-40
-50
0
100
200
300
400
500
600
700
800
900
1000

Fig. 2

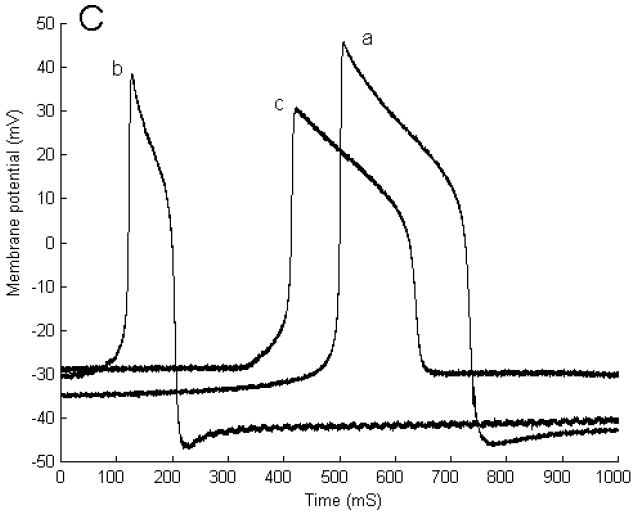

Fig. 2. Effect of two new DHPs and nifedipine on high threshold Ca^{2+} spike. The effect of mebudipine (A), dibudipine (B) and nifedipine (C) on Ca^{2+} spike, before (a), after external application (b) and washout (c). When either two new DHPs or nifedipine were added to the bathing media separately, the peak amplitudes of action potentials (APs) and AHP were reduced and the duration of APs decreased. These inhibitory effects were almost completely reversible with washout

As can be seen in Figure 3A, comparing the absolute effects of these DHP compounds using baseline correction method (subtraction of obtained results in the presence of DHPs from control condition), indicates that there is a significant difference among responses to different drugs in reducing the duration of action potentials (ANOVA : $F(2, 16) = 9.62$, $p<0.01$). LSD test have shown that these new DHP compounds are more effective than nifedipine in reducing the duration of Ca^{2+} spikes. However, there is no significant difference between the effect of mebudipine and dibudipine in decreasing the duration of Ca^{2+} spikes (Fig. 3A). Spontaneous calcium spike was suppressed in the presence of high DHPs concentrations, in order to determine the IC_{50} values, voltage response was elicited following injection of 1 nA depolarizing current under the current clamp condition. Half maximal reduction (IC_{50}) in the duration of evoked Ca^{2+} spike occurred at 2.16×10^{-6} M nifedipine, 2.67×10^{-6} M dibudipine and 5.85×10^{-7} M mebudipine. Statistical analysis of data of Figure 4 and Table I indicates that there is a significant difference between the IC_{50} of mebudipine and that of nifedipine or dibudipine (ANOVA analysis, $p<0.05$). Therefore, the potency of mebodipine is greater than that of nifedipine or dibudipine.

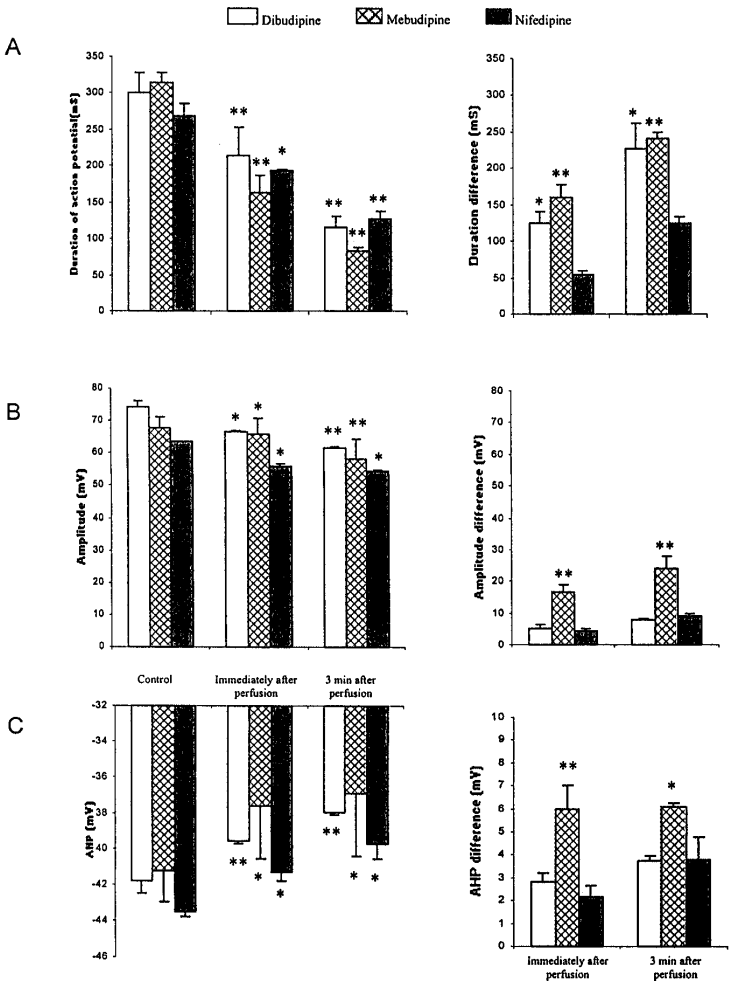

Fig. 3. Effects of DHPs on characteristics of Ca^{2+} spike. Spontaneous Ca^{2+} spike was recorded and F1 neuronal cells were exposed to 1 μM DHPs (mebudipine, dibudipine, or nifedipine) as described in the text. The duration of action potential (A) the peak amplitude of action potential (B) and the after hyperpolarization potential (AHP) (C) were measured and compared statistically immediately or after 3 min of drugs application (left panel). The absolute effects (using baseline correction method) have been shown in the right panel. The effect of DHP compounds on action potential configuration, expressed as the difference between control and after drug application

Values are means ± standard errors of the mean (n = 7 to 35). In the left panel, * is used for $p<0.05$ and **is used for $p<0.01$ compared to control. In the right panel * is used for $p<0.05$ and ** is used for $p<0.01$ compared to the nifedipine

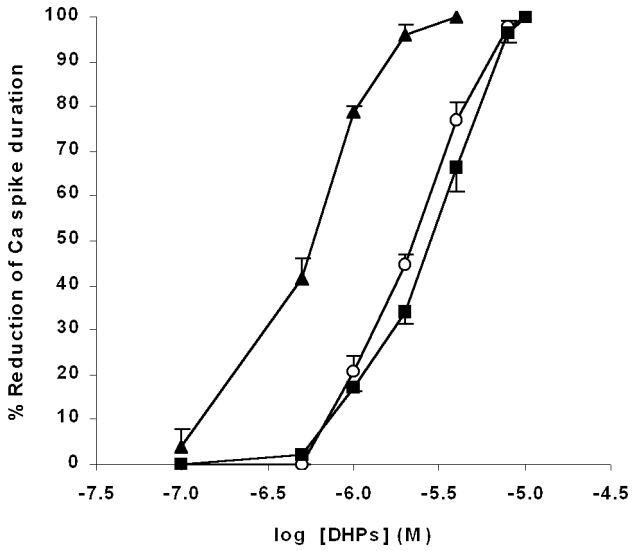

Fig. 4. Concentration dependence of the reduction of duration of Ca^{2+} spike by nifedipine (o), dibudipine (■) and mebudipine (▲). Each point represents the mean ± S.E.M. (n=5)

Table I

Half-maximal reduction (IC_{50}) of duration of Ca^{2+} spike in the presence of nifedipine, dibudipine and mebudipine

Drug	IC50 (M)	Asymptotic 95% confidence interval	
		Lower	Upper
Nifedipine	2.16×10^{-6}	2.00×10^{-6}	2.32×10^{-6}
Dibudipine	2.67×10^{-6}	2.48×10^{-6}	2.87×10^{-6}
Mebudipine	5.85×10^{-7}	5.37×10^{-7}	6.32×10^{-7}

The result in Figure 3B demonstrates the effects of nifedipine, mebudipine, or dibudipine at 1 μM concentration on the amplitude of spontaneous Ca^{2+} action potential. All applied drugs caused a significant decrease in spike amplitude (ANOVA: $F(2,16) = 10.76$, $p<0.01$). Furthermore, the obtained data showed that mebudipine was more effective than dibudipine and nifedipine in decreasing the amplitude of Ca^{2+} spike ($p<0.01$).

However, there was no significant difference between the effects of nifedipine and dibudipine on the amplitude of action potential (Fig. 3B, left panel).

The effect of these three L-type Ca^{2+} channel blockers on the peak amplitude of AHP following the Ca^{2+} spikes was also analyzed. Superfusion of nifedipine, mebudipine or dibudipine produced a significant reduction in the peak amplitude of AHP (ANOVA: $F(2,15) = 7.69$, $p<0.01$). This inhibitory effect of mebudipine was significantly stronger than that of nifedipine and dibudipine ($p<0.01$). However, there was no significant difference between the effect of dibudipine and nifedipine on the peak amplitude of AHP (Fig. 3C). The reversibility of the inhibitory effects of these DHPs was assessed separately after the wash out of these drugs by replacing bathing media containing DHPs with calcium selective Ringer. After 10 min of exposure at a concentration of 1 μM, the depressant actions of mebudipine, dibudipine and nifedipine could be almost completely reversed 10 min after washing (Fig. 2).

In addition, in the presence of normal Ringer, the effects of these DHPs on fast action potential configuration were separately examined. It was found that application of two new calcium channel blockers and nifedipine did not alter the configuration of action potential or the resting membrane potential, but there was a tendency for the reduction of the peak amplitude of action potential.

Discussion

In previous studies it was shown that both mebudipine and dibudipine had comparable pharmacological effects with nifedipine while offering some advantages such as longer biological half life, longer time to reach peak effect and stronger vasoselectivity (especially mebudipine) (20, 22). The present account described the blocking effect of these two new DHPs on high threshold Ca^{2+} spikes in comparison with nifedipine.

Following the blocking of fast Na^+ inward current and addition of 4-AP, the duration of action potential was prolonged. Blockade of 4-AP sensitive current, therefore, enhanced Ca^{2+} conductance and resulted in a large increase in duration (19, 26). Voltage gated potassium channels play a major role in neuronal action potential. In addition to different kinds of fast and delayed rectifier K^+ outward currents (5, 6, 15), a fast Ca^{2+}-activated K^+ current (I_C) also was reported to contribute to action potential repolarization and after hyperpolarization potentials in Helix neurons (11, 12).

It has been reported that 4-AP produced the plateau-like depolarization for extended periods in vertebrates (4, 16, 18) and invertebrates (10). It seemed that interfering with repolarizing potassium currents by 4-AP could cause such a prolonged depolarization because of inward ionic current with Ca^{2+} conductance. In the present study the DHP compounds reduced the duration of Ca^{2+} spikes to a considerable extent, while the effect on the spike amplitude was moderate. Similar result has been reported in hippocampal CA1 pyramidal neurons (17, 19). The results of our previous work on Ca^{2+} channel currents in Helix neurons showed that 55% of Ca^{2+} current was carried by L type and the remaining current by T type (5, 6, 15). Therefore, taken together, when interpreting the effect of DHPs on the rate of rise and maximum amplitude of Ca^{2+} spikes, the existence of T type calcium channel has to be taken into account (5, 12). So,

the reason that the maximum amplitude and action potential rate of rise did not change dramatically in comparison with duration, could be due to unmasked T and/or possibly N type calcium inward currents which show a fast activation and inactivation kinetics in comparison with L-type.

In fact the balance between calcium and potassium current will determine the rate of repolarization and therefore the shape (especially the duration) of the action potential. The results of this study suggest that DHPs compounds can have profound effect on action potential shape in F1 neurons possibly through their effect on the L-type Ca^{2+} currents.

Nifedipine has been reported to block L-type Ca^{2+} channel current in *Helix aspersa* neurons (14). Therefore, dramatic decrease in the duration of Ca^{2+} spikes either in presence of two new DHPs or nifedipine is mainly due to blockage of L-type Ca^{2+} channels. It is stated that with ethanol as a solvent, nifedipine has no effect on the T-type channel current (2, 18).

It has been reported that asymmetric esters of dihydropyridines are generally more potent than symmetric esters (9, 24). The results of the previous studies (20, 22) and current study are in agreement with this, since the effect of mebudipine in reducing the duration of action potentials is more potent than dibudipine and nifedipine (Fig. 4 and Table I).

In addition, external application of mebudipine, dibudipine or nifedipine resulted in a remarkable reduction of the amplitude of AHPs, while the potency of mebudipine in eliciting this effect was greater than that of dibudipine or nifedipine (Fig. 3C). The AHP that follows action potentials is an important intrinsic negative feedback mechanism controlling excitability. The AHP is generated by activation of distinct types of outward K^+ channels by Ca^{2+} ions entering the neuron during an action potential (8, 21, 25, 27). In addition to inhibiting Ca^{2+} channels, it has been stated that DHP Ca^{2+} channel antagonists also inhibit some types of voltage sensitive K^+ channels in both vertebrate and invertebrate cells (13, 23, 32). In this study, the reduction in AHP amplitude could be due to the blockage of Ca^{2+} channels or voltage sensitive outward K^+ channels. The question whether these new Ca^{2+} antagonists cause a specific inhibitory action on the pure Ca^{2+} L-type channels or a non-specific inhibitory action via voltage dependent outward K^+ current deserves further study using the voltage clamp technique.

Somatic voltage recordings in calcium Ringer and in the presence of K^+ channel blockers (4-AP and TEA) revealed that the duration of the action potential was increased and Ca^{2+} blockers reduced it dramatically. There was, on the other hand, no change in the duration of Ca^{2+} spike in the presence of either DHPs in normal Ringer. Reduction of outward K^+ and inward Na^+ currents unmasks the inward Ca^{2+} channel currents (primarily T and L) and results in the broadness of Ca^{2+} spikes (15, 16).

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REFERENCES

1. Almers W, Fink R, Palade PT: Calcium depletion in frog muscle tubules: the decline of calcium current under maintained depolarization. J. Physiol. 312, 177–207 (1981)
2. Angstadt JD, Friesen WO: Synchronized oscillatory activity in leach neurons induced by calcium channel blockers. J. Neurophysiol. 66, 1858–1873 (1991)
3. Arreola J, Calvo J, Garcia MC, Sonchez JA: Modulation of calcium channels of skeletal muscle fibers of the frog by adrenaline and cyclic adenosine monophosphate. J. Physiol. 397, 307–330 (1987)
4. Aubry A, Batini C, Billard JM, Kado RT, Morian P: Tetrodotoxin induced calcium spikes: in vitro and in vivo studies of normal and different Purkinje cells. Exp. Brain Res. 84, 294–302 (1991)
5. Bal R, Janahmadi M, Green GGR, Sanders DJ: Effect of calcium channel blockers on transient outward current of F76 and D1 neuronal soma membrane in the subesophageal ganglion of *Helix aspersa*. J. Membr. Biol. 173, 179–185 (2000)
6. Bal R, Janahmadi M, Green GGR, Sanders DJ: Two kinds of transient outward currents, I_A and I_{Adepol} in F76 and D1 soma membrane of the subesophageal ganglia of *Helix aspersa*. J. Membr. Biol. 179, 71–78 (2001)
7. Bean BP: Classes of calcium channels in vertebrate cells. Annu. Rev. Physiol. 51, 367–384 (1989)
8. Brown DA: Ionic channels and their regulation by G proteins. Annu. Rev. Physiol. 52, 197–213 (1990)
9. Cohen CJ, McCarthy RT: Nimodipine block of calcium channels in rat anterior pituitary cells. J. Physiol. (Lond.) 387, 195–225 (1987)
10. Crest M, Ehile E, Pin T, Watanabe K, Gola M: Plateau-generating nerve cells in *Helix*: properties of the repolarizing voltage-gated and Ca^{2+}-activated potassium currents. J. Exp. Biol. 152, 211–241 (1990)
11. Crest M, Gola M: Large conductance Ca^{2+}-activated K^+ channels are involved in both spike shaping and firing regulation in Helix neurons. J. Physiol. (Lond.) 465, 265–287 (1993)
12. Gola M, Ducreux C, Changneux H: Ca^{2+}-activated K^+ current involvement in neuronal function revealed by in situ single-channel analysis in Helix neurons. J. Physiol. (Lond.) 420, 73–109 (1990)
13. Hume JR: Comparative interaction of organic Ca^{2+} channel antagonists with myocardial Ca^{2+} and K^+ channels. J. Pharmacol. Exp. Ther. 234, 134–140 (1985)
14. Janahmadi M, Bal R, Sanders DJ, Green GGR: Calcium currents in cultured neurons of *Helix aspersa*. J. Physiol. 487–57 (1995)
15. Janahmadi M: Ionic currents in *Helix aspersa* neurones. PhD thesis: University of Newcastle upon Tyne (1996)
16. Kerkut GA, Lambert JDC, Gayton RJ, Loker JE, Walker RJ: Mapping of nerve cells in the sub-eosophageal ganglia of *Helix aspersa*. Comp. Biochem. and Physiol. 50A, 1–25 (1975)
17. Kita T, Kita H, Kitai ST: Effects of 4-aminopyridine (4-AP) on rat neostriatal neurons in an in vitro slice preparation. Brain Res. 361, 1–8 (1985)
18. Lingyun Wu, Karpinski E, Wang R, Pang PK: Modification by solvents of the action of nifedipine on calcium channel currents in neuroblastoma cells. Naunyn. Schemiedberg's Arc. Pharmacol. 345, 478–484 (1992)
19. Magee JC, Carruth M: Dendritic voltage-gated ion channels regulating the action potential firing mode of hippocampal CA1 pyramidal neurons. J. Neurophysiology 82,1895–1901 (1999)
20. Mahmoudian M, Mirkhani H, Nehardani Z, Ghiaee S: Synthesis and biological activity of two new calcium-channel blockers, mebudipine and dibudipine. J. Pharm. Pharmacol. 49, 1229–1233 (1997)

21. Marrion NV, Tavalin SJ: Selective activation of Ca^{2+}-activated K^+ cannels by co-localized Ca^{2+} channels in hippocampal neurons. Nature 395, 900–905 (1998)
22. Mirkhani H, Omrani GR, Ghiaee S, Mahmoudian M: Effects of mebudipine and dibudipine, two new calcium channel blockers, on rat left atrium, rat blood pressure and human internal mammary artery. J. Pharmacol. 51, 617–622 (1999)
23. Nerbonne JM, Gurney AM: Blockade of Ca^{2+} and K^+ currents in bag cell neurons of *Aplysia californa* by dihydropyridine Ca^{2+} antagonists. J. Neurosci. 7, 382–893 (1987)
24. Ohtuska M, Yokota M, Kodama I, Yamada K, Shibata S: New generation dihydropyridine calcium entry blockers: In search of greater selectivity for one tissue subtype. Gen. Pharmacol. 20, 539–556 (1989)
25. Sah P: Ca^{2+}-activated K^+ currents in neurons: types, physiological roles and modulation. Trends in Neurosci. 4, 150–154 (1996)
26. Seo WS, Shin JH, Suh CK: 4-Aminopyridine (4-AP) augments Ca^{2+} dependent action potential and changes oscillatory firing patterns in rat cerebellar Purkinje cells. Yonsei Medical J. 40, 112–117 (1999)
27. Storm JF: An after-hyperpolarization of medium duration in rat hippocampal pyramidal cells. J. Physiol. 409, 171–190 (1980)
28. Sundgren-Anderson AK, Johansson S: Calcium spikes and calcium currents in neurons from the medial preoptic nucleus of rat. Brain Res. 783, 194–209 (1998)
29. Swandulla D, Carbone E, Lux HD: Do calcium channel calssification account for neuronal calcium channel diversity? Trends in Neurosci. 14(2), 46–51 (1991)
30. Taylor PS: Selectivity and patch measurement of A-current in *Helix aspersa* neurons. J. Physiol. 388, 437–447 (1987)
31. Tennigkeit F, Schwarz DW, Puil E: Modulation of bursts and high-threshold calcium spikes in neurons of rat auditory thalamus. Neurosci. 83, 1063–1073 (1998)
32. Valmier J, Richard S, Dric E, Nargeot J, Simonneau M, Baldy-Moulinier M: Dihydropyridines interact with calcium-independent potassium currents in embryonic mammalian sensory neurons. Pfluegers Arch. 419, 281–287 (1991)