

# Dendritic BK Channels activation by N-type voltage-gated $\text{Ca}^{2+}$ channels in neocortical layer-5 pyramidal neurons

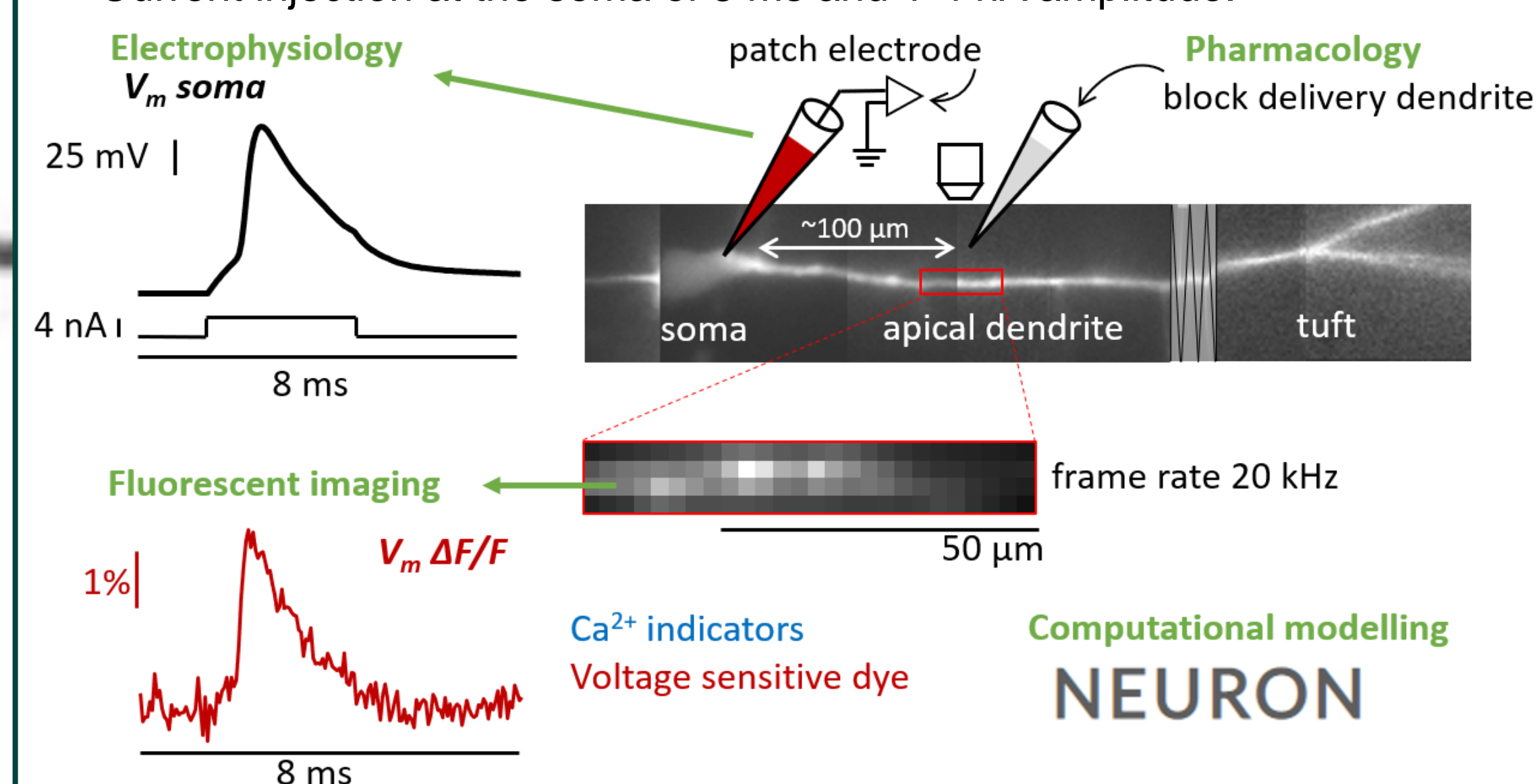
## INTRODUCTION

The action potential (AP) generated in the axon actively back-propagates (bAP) into the dendrites through the sequential activation and deactivation of diverse ion channels. Here, using ultrafast membrane potential ( $V_m$ ) and  $\text{Ca}^{2+}$  imaging, we show that N-type voltage-gated  $\text{Ca}^{2+}$  channels (VGCCs) in the apical dendrite of layer-5 neocortical pyramidal neurons, selectively target large-conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels (BK CAKCs). We show that this BK CAKC activation occurs within 500  $\mu\text{s}$  following the AP peak, i.e. before the peak of the  $\text{Ca}^{2+}$  current elicited by the AP. This way, when N-type VGCCs are inhibited, the early widening of the AP shape boosts the other activated VGCCs increasing the total  $\text{Ca}^{2+}$  influx. We built a realistic NEURON model showing that a strong coupling between N-type and BK channels is necessary to reproduce the experimental results.

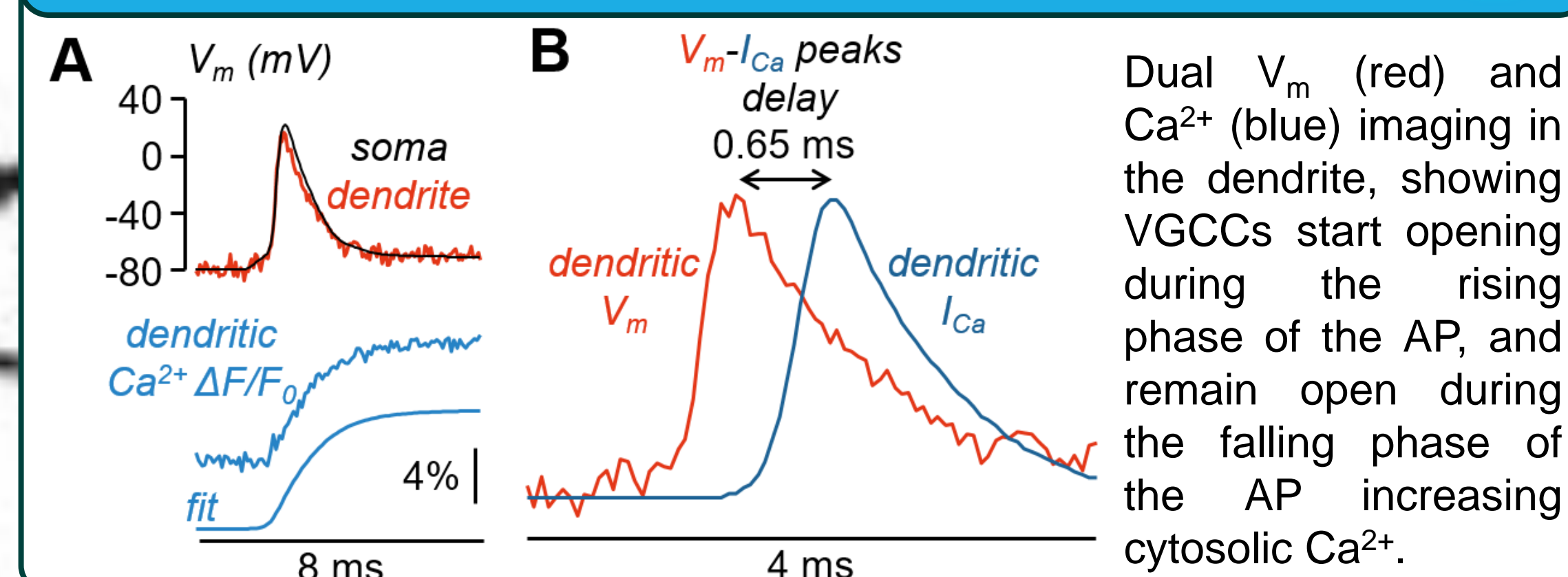
## METHODS

### Electrophysiology

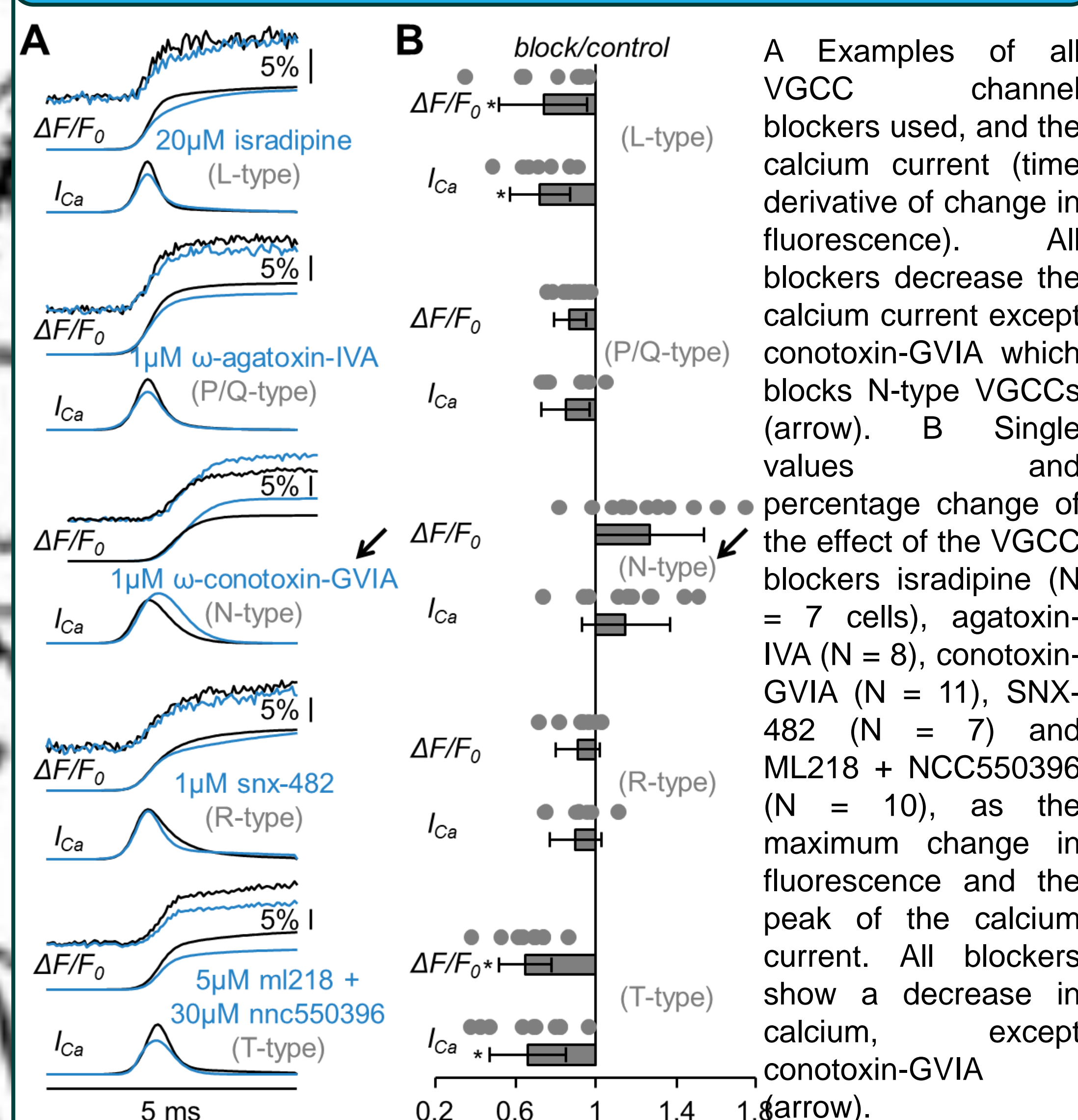
- Sagittal 350  $\mu\text{m}$  cortical brain slices from P21-35 C57Bl/6j mice.
- L5 somatosensory pyramidal neurons in whole-cell patches filled with voltage sensitive dye JPW1114 or a calcium indicator (OG5N or CAL-520FF).
- Current injection at the soma of 3 ms and 1-4 nA amplitude.



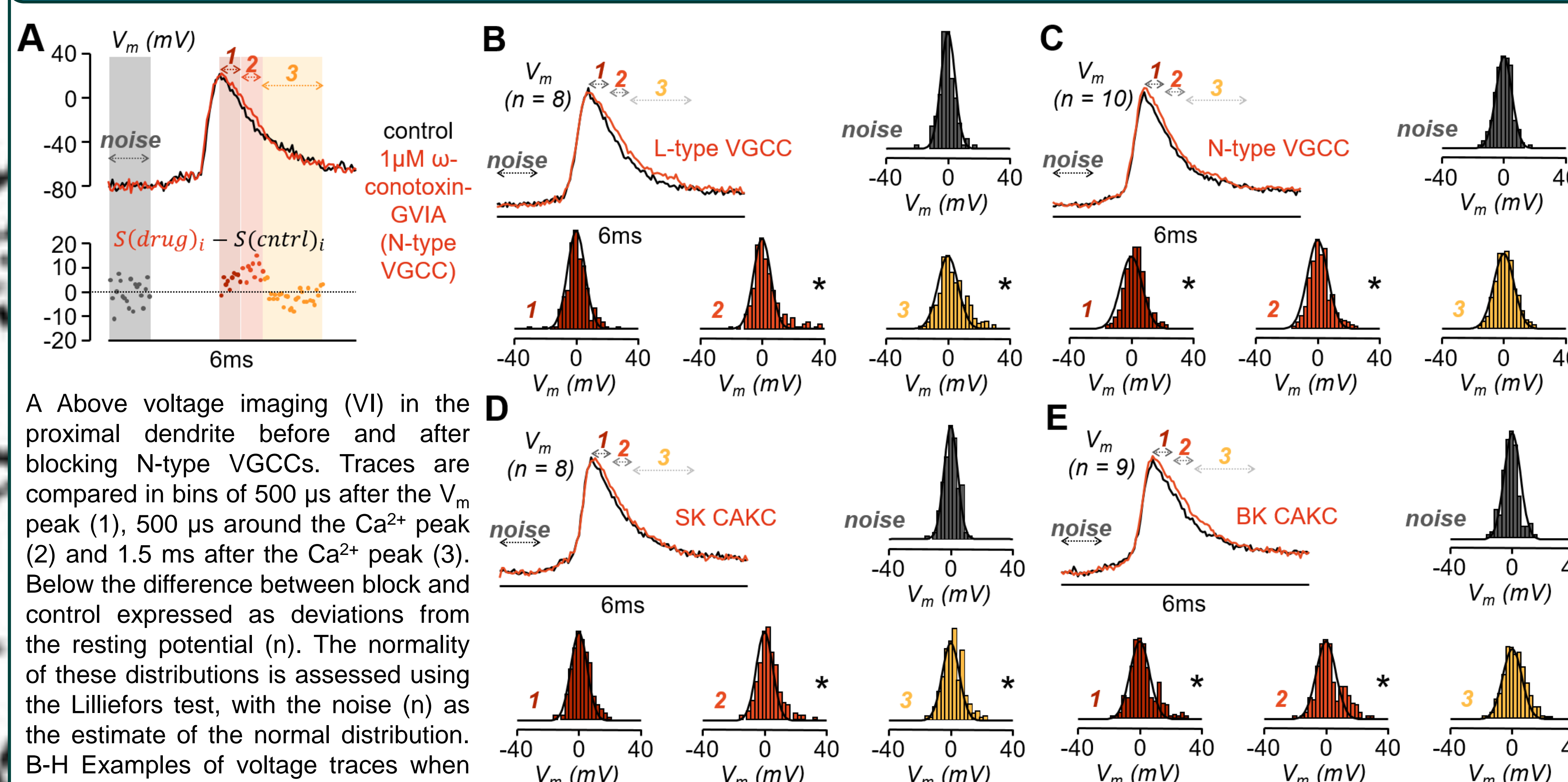
## The inward $I_{\text{Ca}}$ -peak is delayed compared to the bAP-peak



## Blocking N-type VGCCs increases $\text{Ca}^{2+}$ influx during a bAP

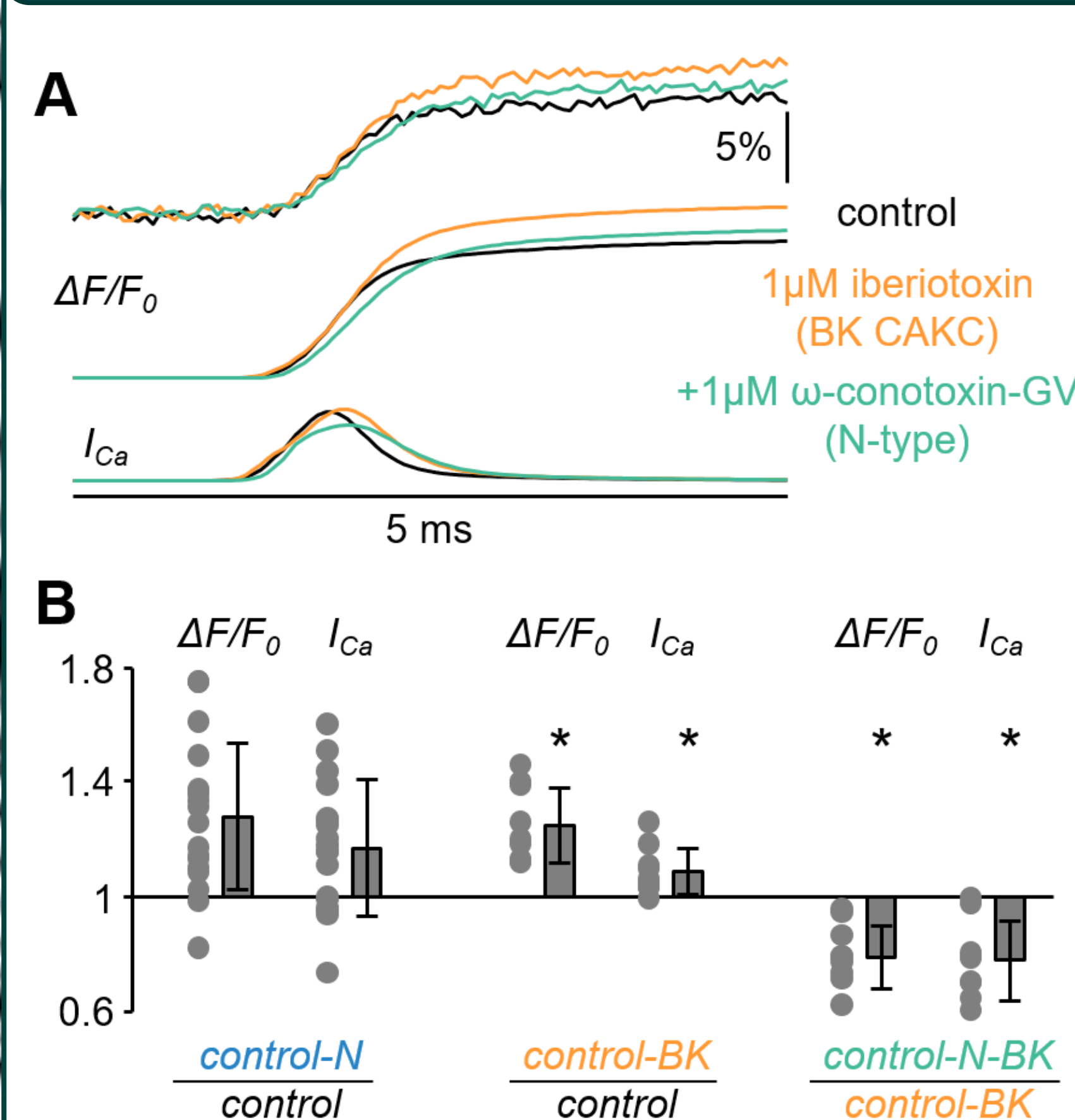


## The effect of N-type VGCC and BK CAKC coupling occurs in the first 500 $\mu\text{s}$ after the AP peak

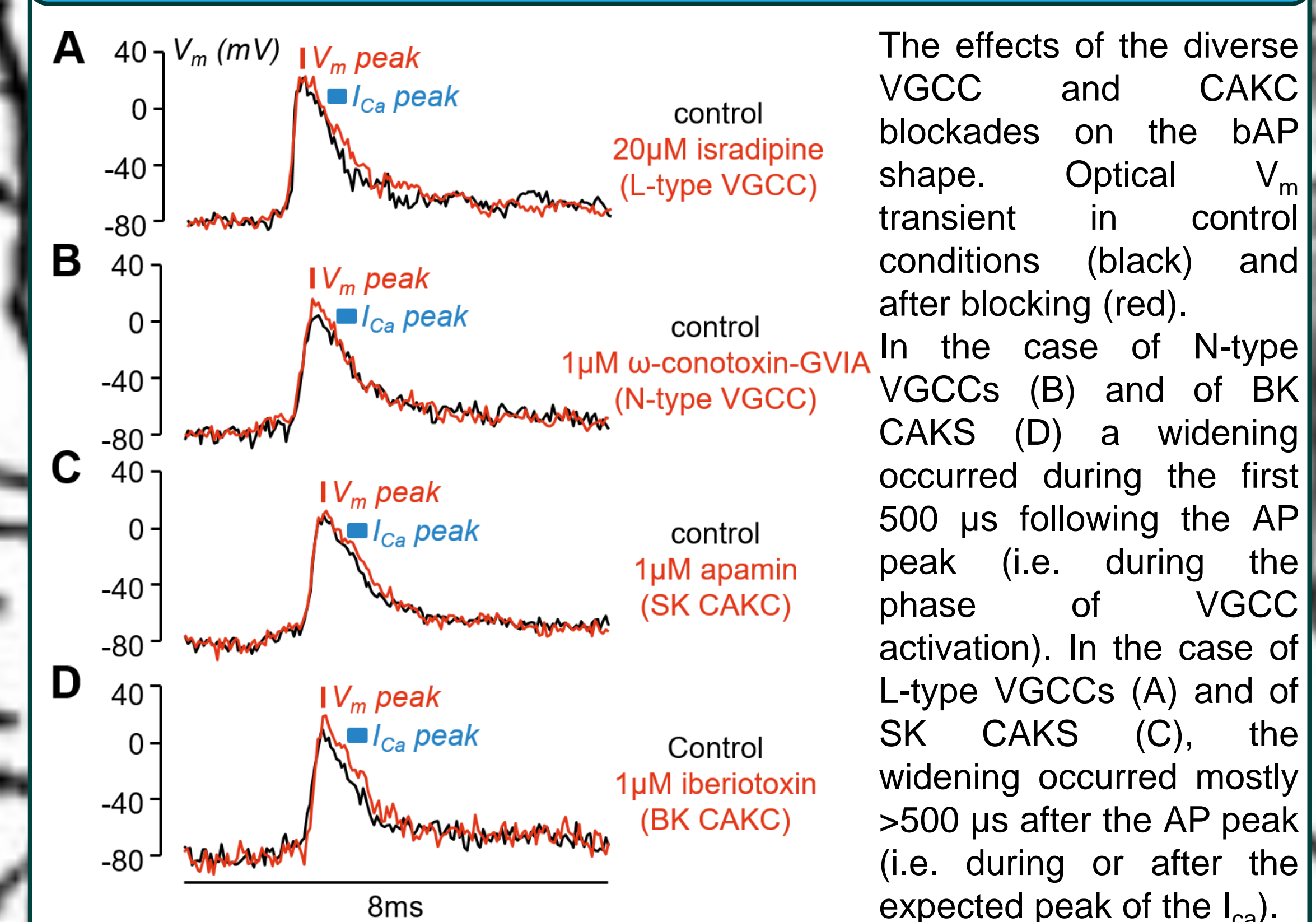


P-values are calculated using the Lilliefors test (based on the Kolomogorov-Smirnov test), which determines if the data follows a normal distribution when the parameters of the normal distribution are unknown.

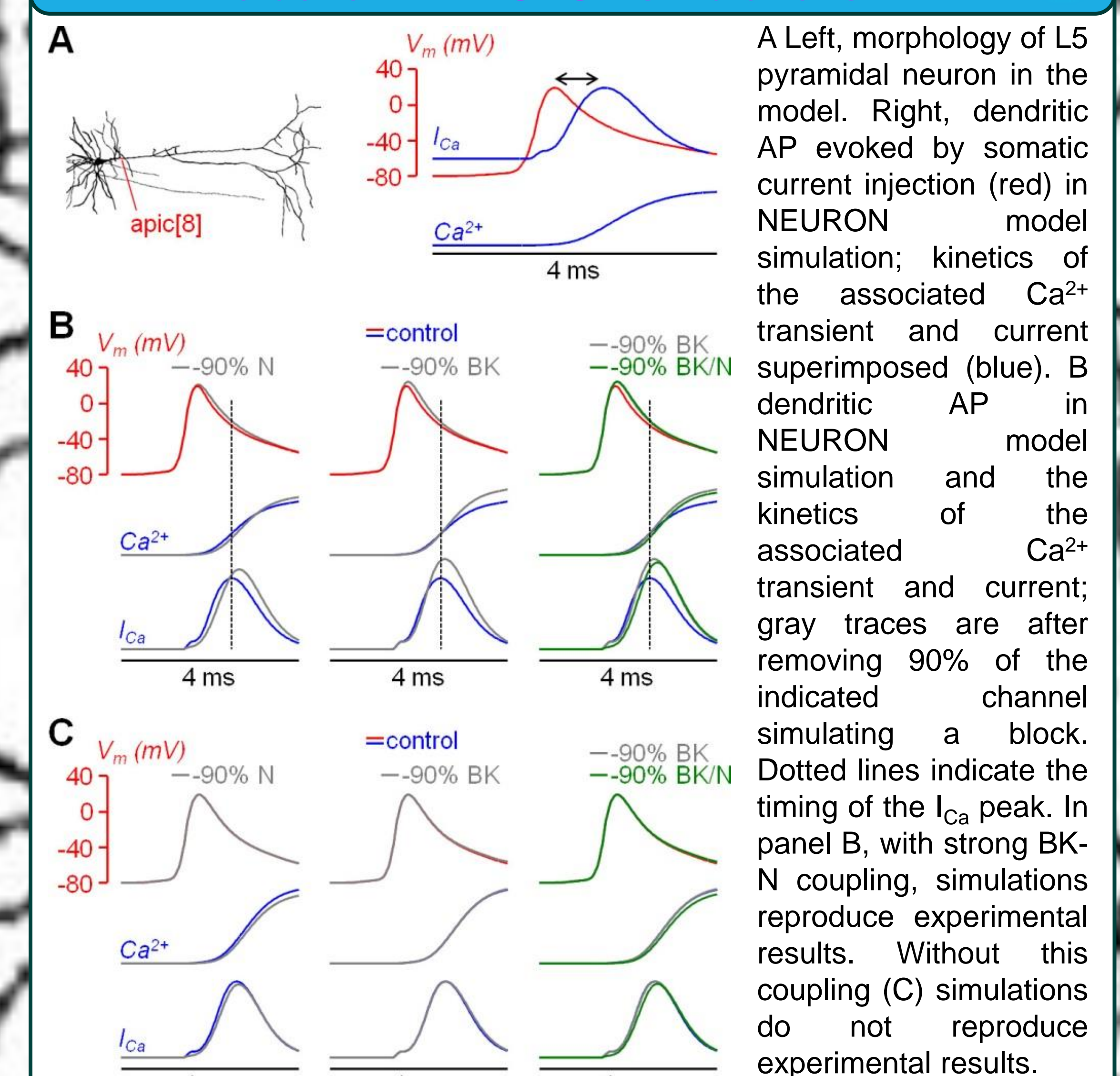
## BK CAKCs are activated by $\text{Ca}^{2+}$ influx through N-type VGCCs during a bAP



## Blocking N-type VGCCs increases the peak of the bAP



## Reproduction of BK and N-type VGCCs interaction in NEURON simulations



## CONCLUSION

N-type VGCCs have an exclusive specific role in neuronal dendrites as activator of BK CAKCs. N-type activation is rapid and is not linear with the increase of intracellular  $\text{Ca}^{2+}$  concentration associated with the transient activation of VGCCs. Thus, the blockade of N-type VGCCs widens the AP peak prolonging  $\text{Ca}^{2+}$  entry through the other VGCCs and boosting the increase of intracellular  $\text{Ca}^{2+}$  concentration associated with the AP.