BK channels promote bursting in pituitary cells

1) Background on pituitary cells and BK channels
2) Experimental evidence and its problems
3) Modeling evidence and its problems
4) Using the dynamic clamp to prove the point
The anterior pituitary gland
Calcium influx induces hormone secretion

(from Stojilkovic et al 2005)
Pituitary cells differ in their basal activity

Why are gonadotrophs different?

Van Goor et al (2001a)
Gonadotrophs lack large potassium (BK) current

Van Goor et al (2001b)
Can the difference in electrical activity be explained by differences in BK channel expression?
BK channels usually have an opposite effect

BK channels
- Large conductance (B = Big)
- Calcium- and voltage-dependent
- Activated by inhibitory hormones

Rat chromaffin cells
(Vandael et al 2010)
BK channels can associate with Ca\textsuperscript{2+} channels to produce fast activating outward current

Berkefeld et al (2010)
Blocking BK channels switches the activity pattern from bursting to spiking

Somatotroph recordings

Van Goor et al (2001c)
Problems with blocking experiments

- Blocking a channel can change the system
- BK channels may be necessary for bursting -- but what do they do?
- Which BK channels promote bursting?

Transition to spiking after BK block:
Due to block of fast (V-dependent) component or block of slow (Ca-dependent) component?
Lactotroph model

\[ C \frac{dV}{dt} = g_{Ca} m_x(V)(V_{Ca} - V) + g_K n(V_k - V) + g_{SK} \frac{[Ca]^2}{[Ca]^{2} + k^2} (V_k - V) - I_{BK} \]

\[ \tau_n \frac{dn}{dt} = n_x(V) - n \]

\[ \tau_{Ca} \frac{d[Ca]}{dt} = -(c I_{Ca} + k_c [Ca]) \]

I_K(V) kinetics (\(\tau_n\)) chosen so that the model is spiking

\[ I_{BK}(V) = g_{BK} f(V - V_K) \]

→ bursting?
BK channels change the activity pattern of a pituitary cell model from spiking to bursting.

Channel activation must be fast.
$I_{BK}$ promotes “depolarization block”

**fast/slow analysis**

$V, n$ fast  
$[Ca]$ slow

This explains why $BK$ activation must be fast
Problems with the model

BK channels change activity from spiking to bursting in THIS model.

What if we use different parameters or include a more realistic set of channels?

Nevertheless the model makes an important prediction: BK channel activation must be fast
BK channels have a robust burst promoting effect on pituitary cell models but BK channels are not necessary for bursting.

512 models ± 50% variations in parameter values
Dynamic clamp: one small step for a setup, one giant leap forward for electrophysiology

Original concept: Sharp et al 1993
Implementation: QuB (Milescu et al 2008)

**Patch clamp amplifier**
(current clamp)

**Digitizer**

**Computer**

\[
\frac{df}{dt} = \frac{f_{\infty}(V) - V}{\tau_{BK}}
\]

\[
I_{BK} = g_{BK} \times f \times (V - V_K)
\]

\( I_{BK} \)
Adding back $I_{BK}(V)$ with dynamic clamp restores bursting GH4 cells (lacto-somatotroph cell line).

Perforated patch
BK block decreases burstiness in 11/13 cells.
Subtracting $I_{BK}$ converts bursting into spiking
BK current correlates with cell burstiness

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**Graphs:**

- Top graph: Traces of BK current ($I_{BK}$) over time (ms) with early and late epochs indicated.
- Bottom left graph: Scatter plot of early $I_{BK}$ against cell burstiness, with a correlation coefficient $r = 0.74$.
- Bottom right graph: Scatter plot of late $I_{BK}$ against cell burstiness, with a correlation coefficient $r = 0.12$. 

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$I_{BK}$ must activate rapidly to restore bursting
Can BK channels transform spiking gonadotrophs into bursters?
\( I_{BK} \) switches the activity of gonadotrophs from spiking to bursting.
Summary of results

• BK channels do promote bursting in pituitary cells.
• Their activation/deactivation must be fast -- they must be closely associated with calcium channels.
• Hormonal signals may modulate BK channels and other channels, so BK effect (stimulatory or inhibitory) may depend on physiological status.
The dynamic clamp technique can overcome limitations of experimental techniques and modeling by bridging them together.

It is easy to implement. If you can do current- and voltage-clamp, you can do dynamic clamp.

It is cheap (if you already have a patch setup)
Collaborators

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