Regulation of biphasic and pulsatile insulin secretion

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Myriam Nenquin Magalie Ravier

Nobuyoshi Ishiyama Patrick Stiernet Andras Szollosi

Bo Ahren Joseph Bryan Paolo Meda Susumu Seino

Northern Greece Diabetes Association **Thessaloniki, 8-9 May 2009**

Glucose-induced insulin secretion : control mechanisms

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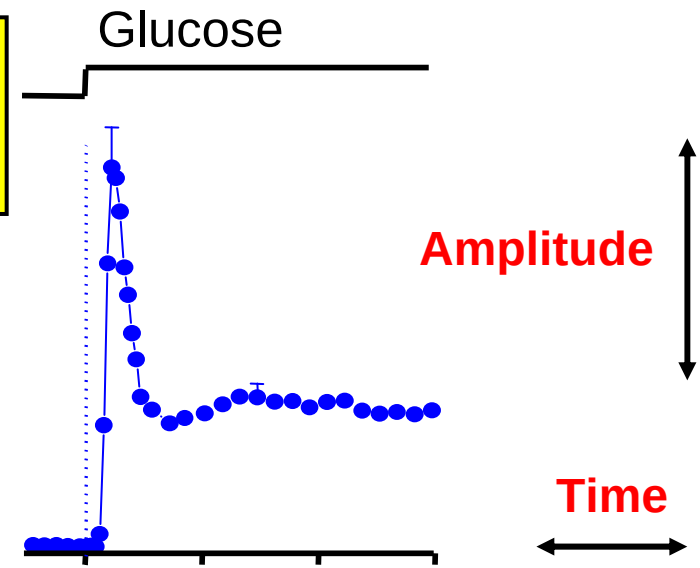
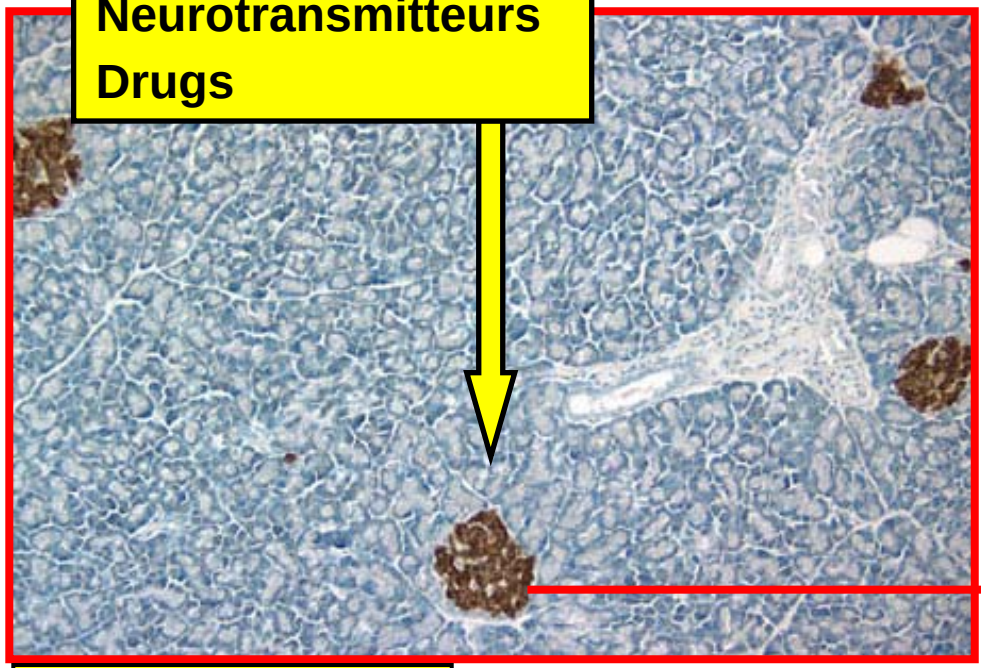
Insulin secretion by mouse islets



Glucose

Other nutrients
Hormones
Neurotransmitteurs
Drugs

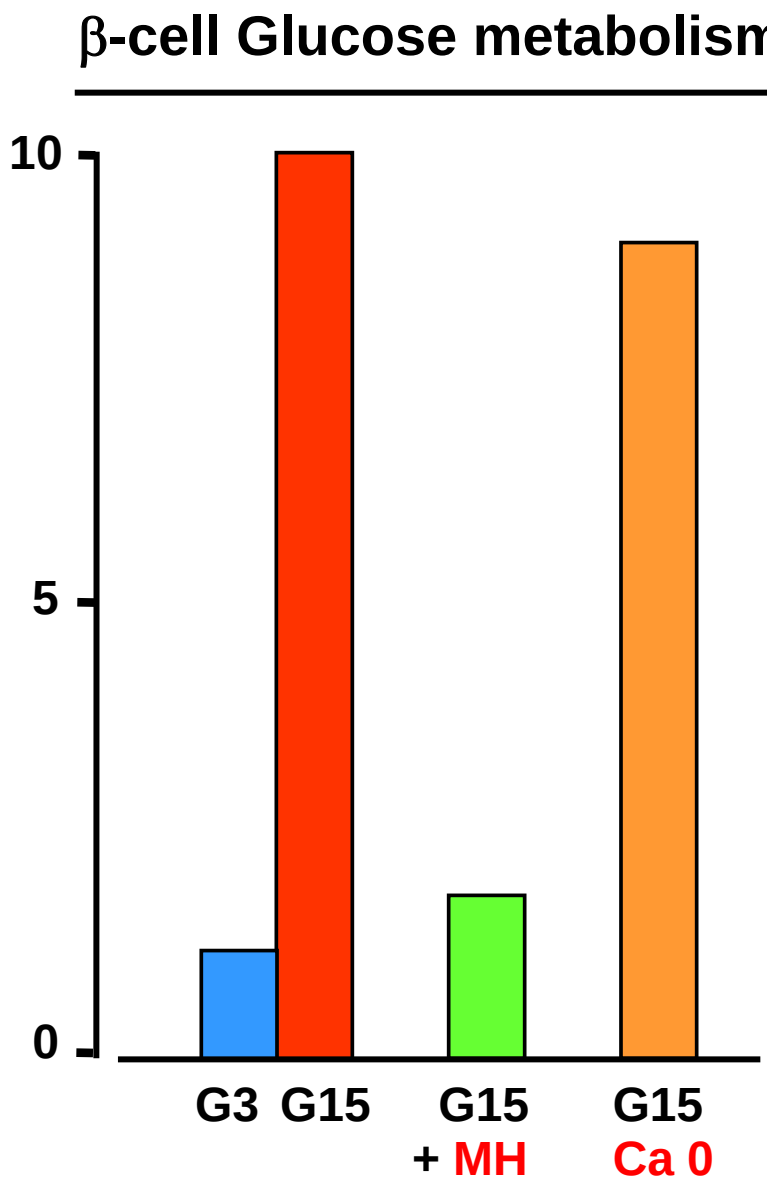


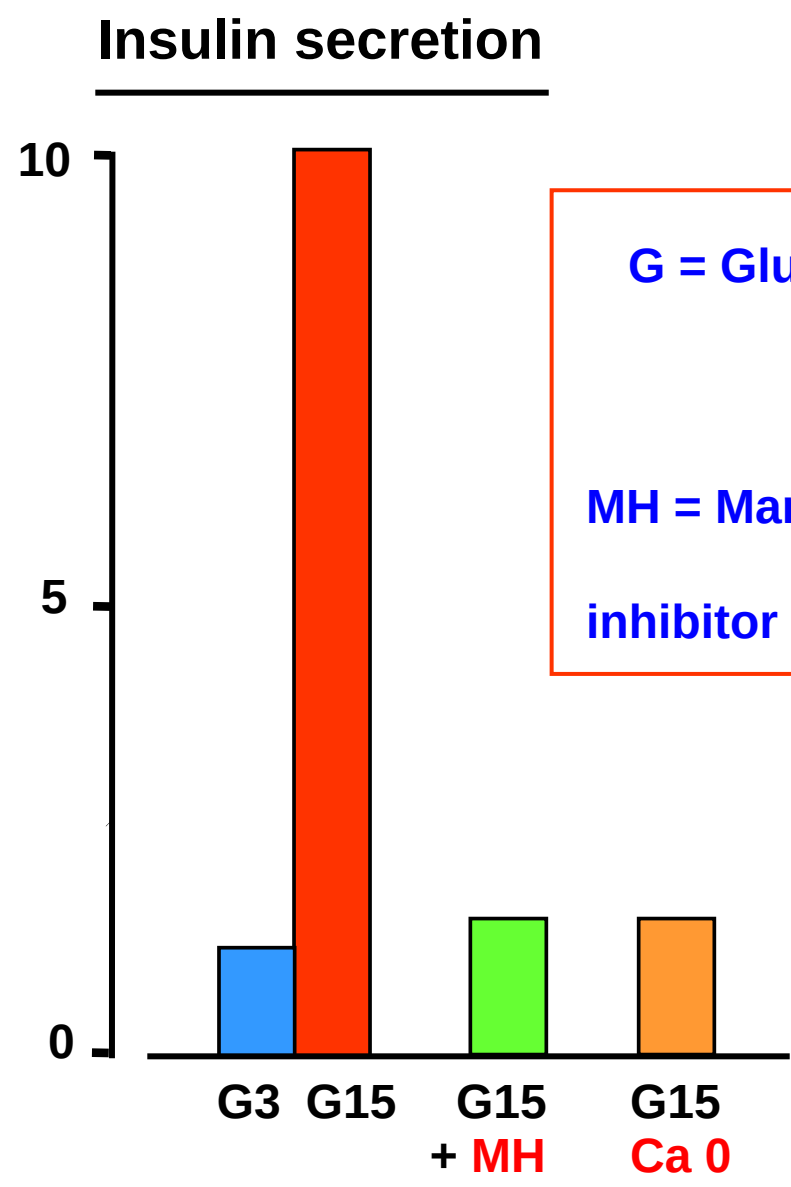
Islets in pancreas

Insulin granules

The bases of a consensus model of glucose-induced insulin secretion

Glucose-induced insulin secretion depends on metabolism and Ca





G = Glucose in mM

MH = Mannoheptulose

inhibitor of Glucokinase

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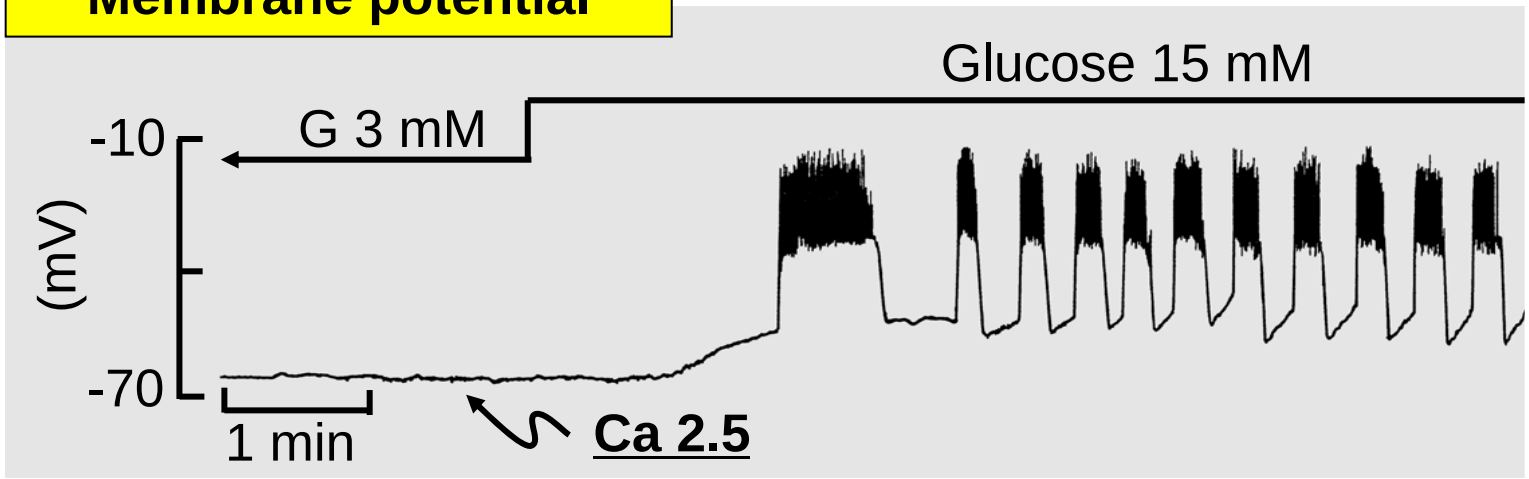
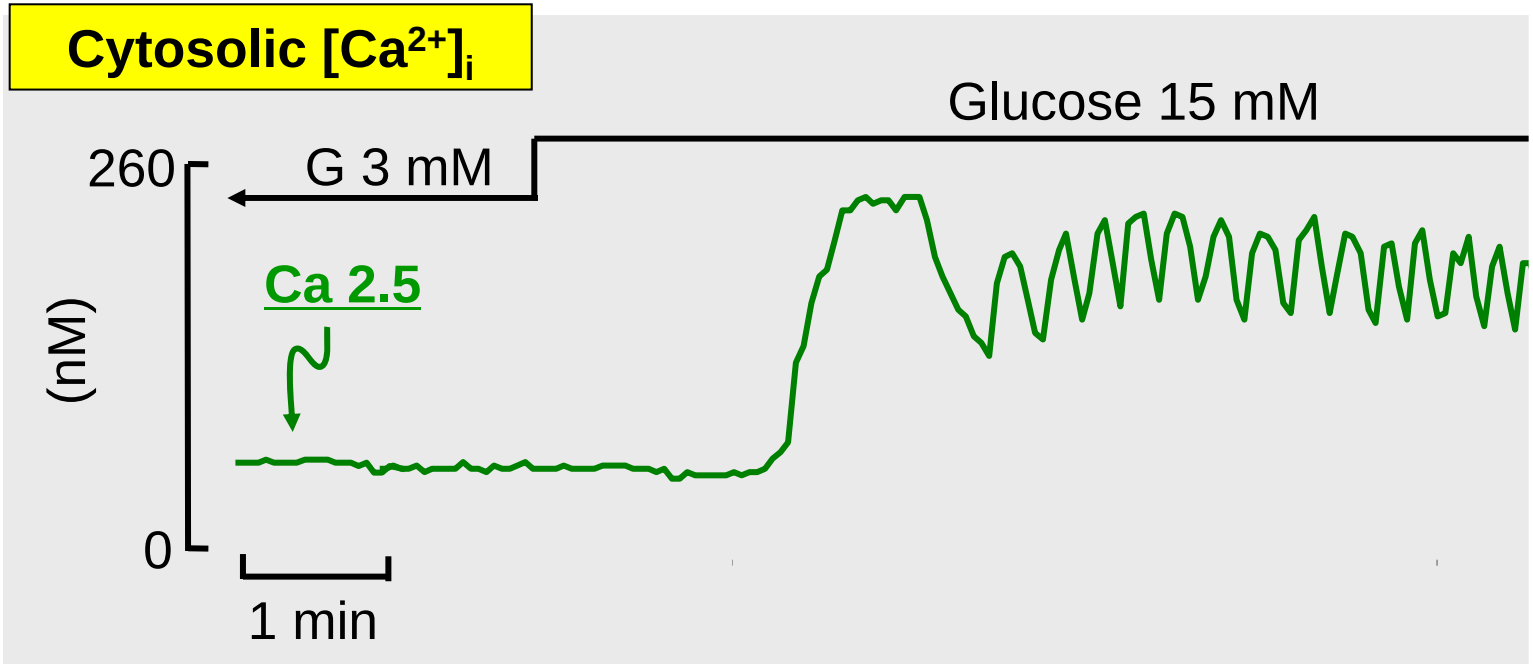
Effects of glucose on β-cell membrane potential and $[Ca^{2+}]_i$

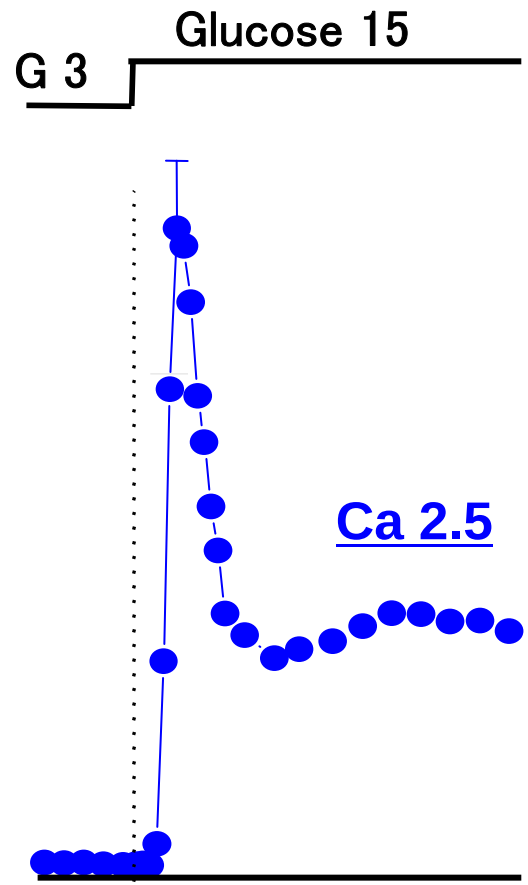
Membrane potential



Cytosolic $[Ca^{2+}]_i$



Insulin secretion



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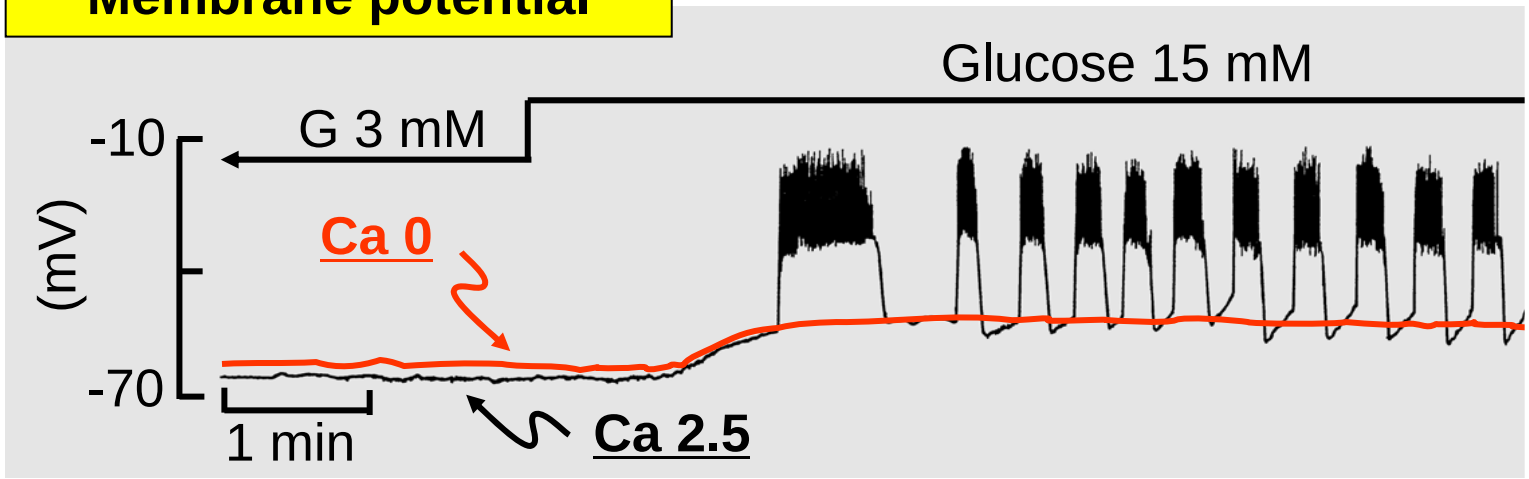
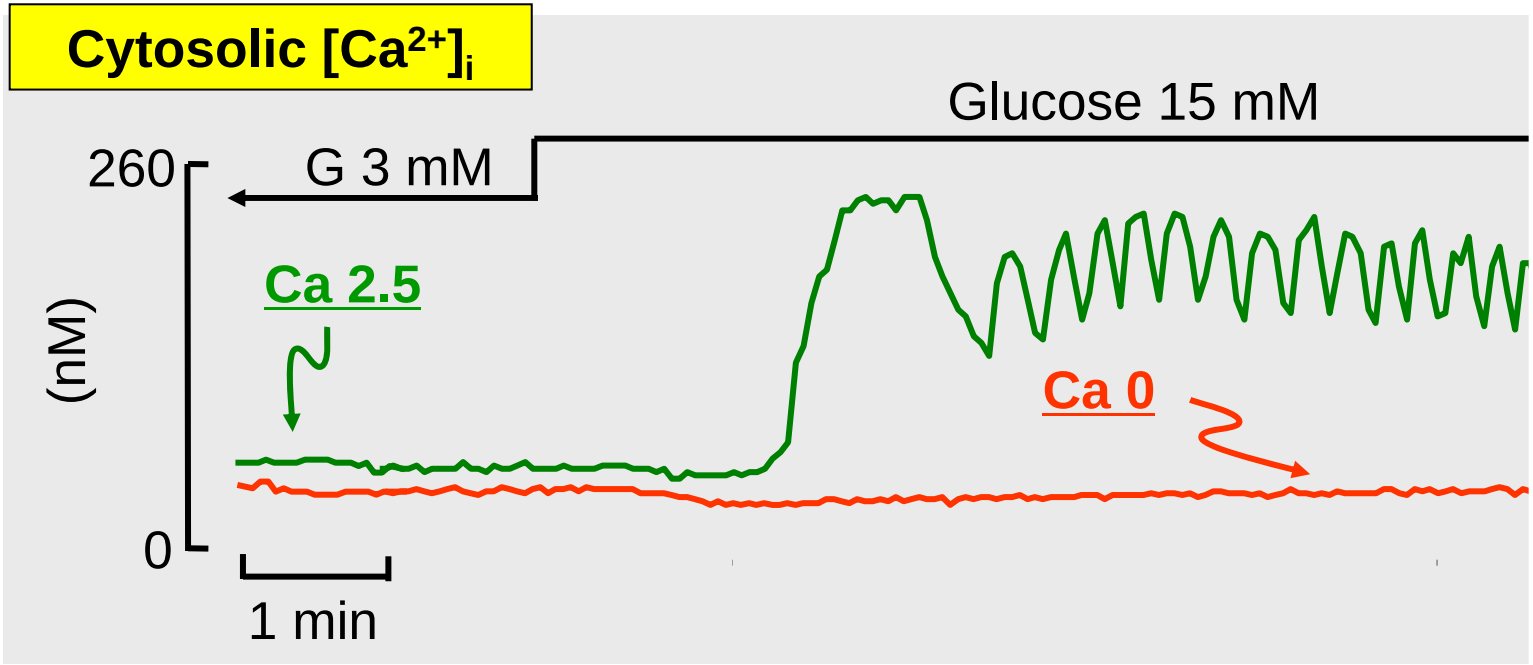
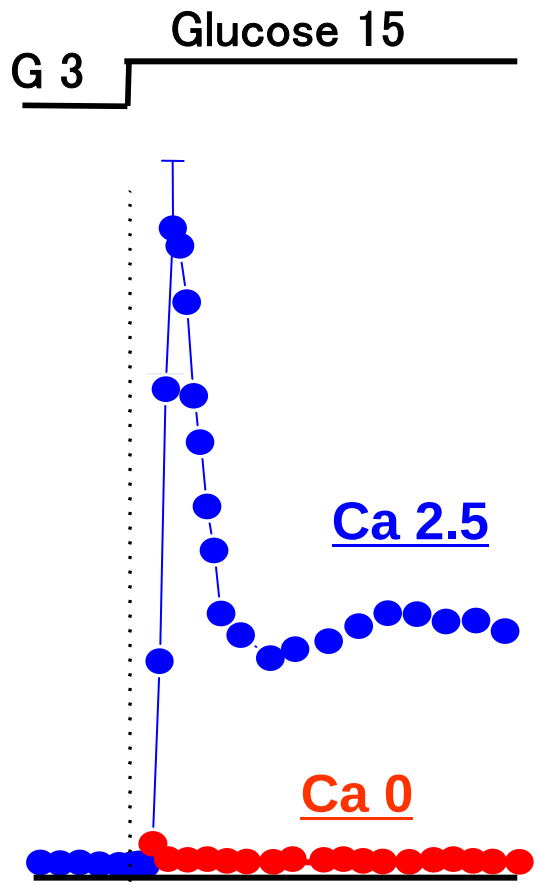


Cytosolic $[Ca^{2+}]_i$



Insulin secretion



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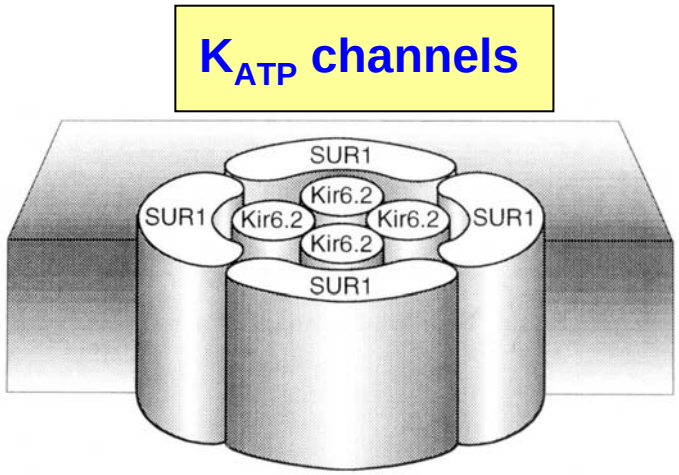
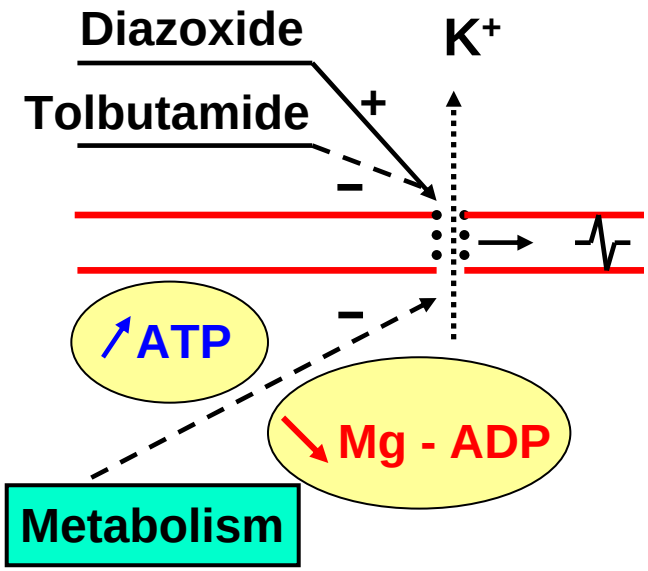
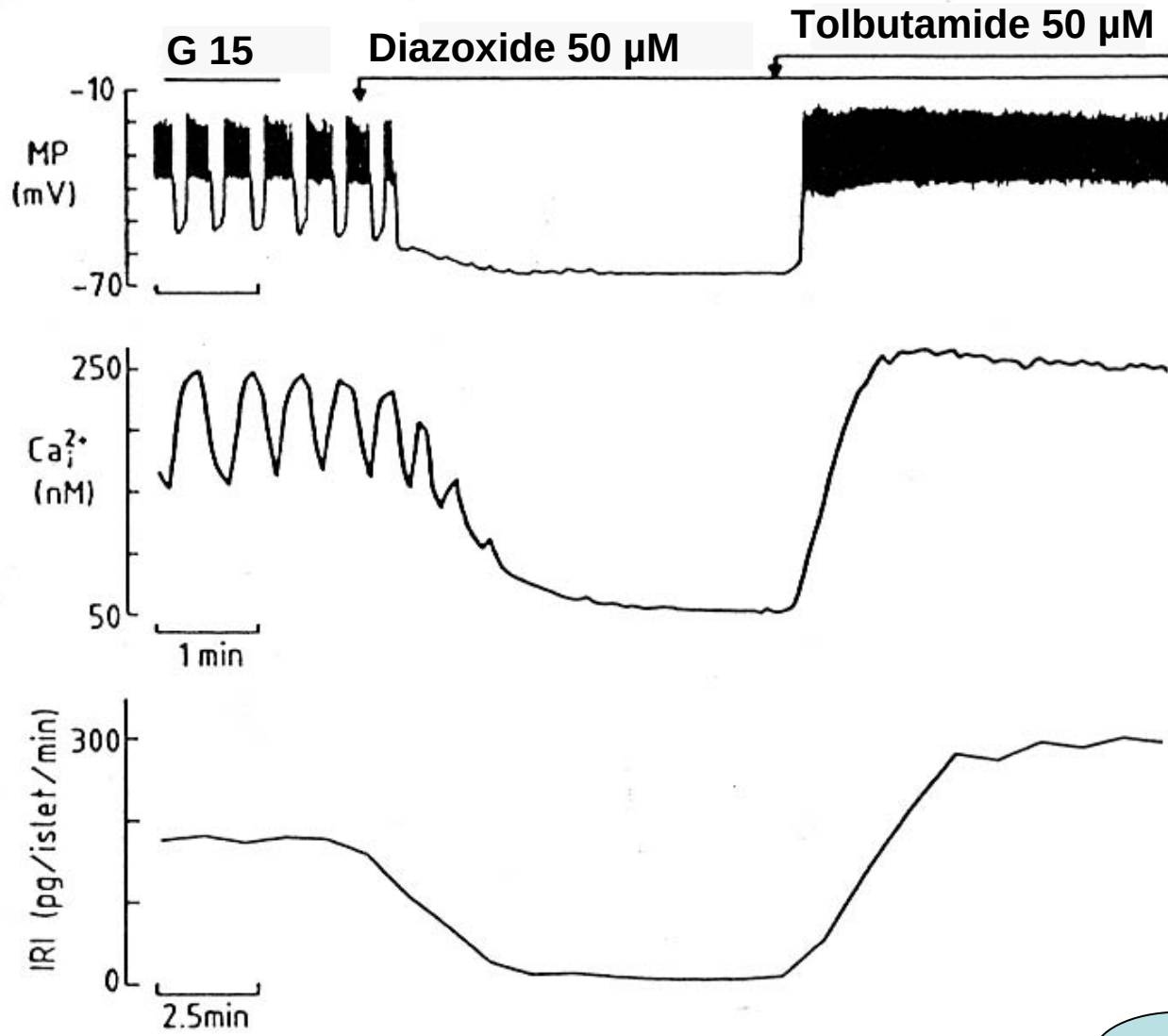
Role of K_{ATP} channels in glucose-induced insulin secretion







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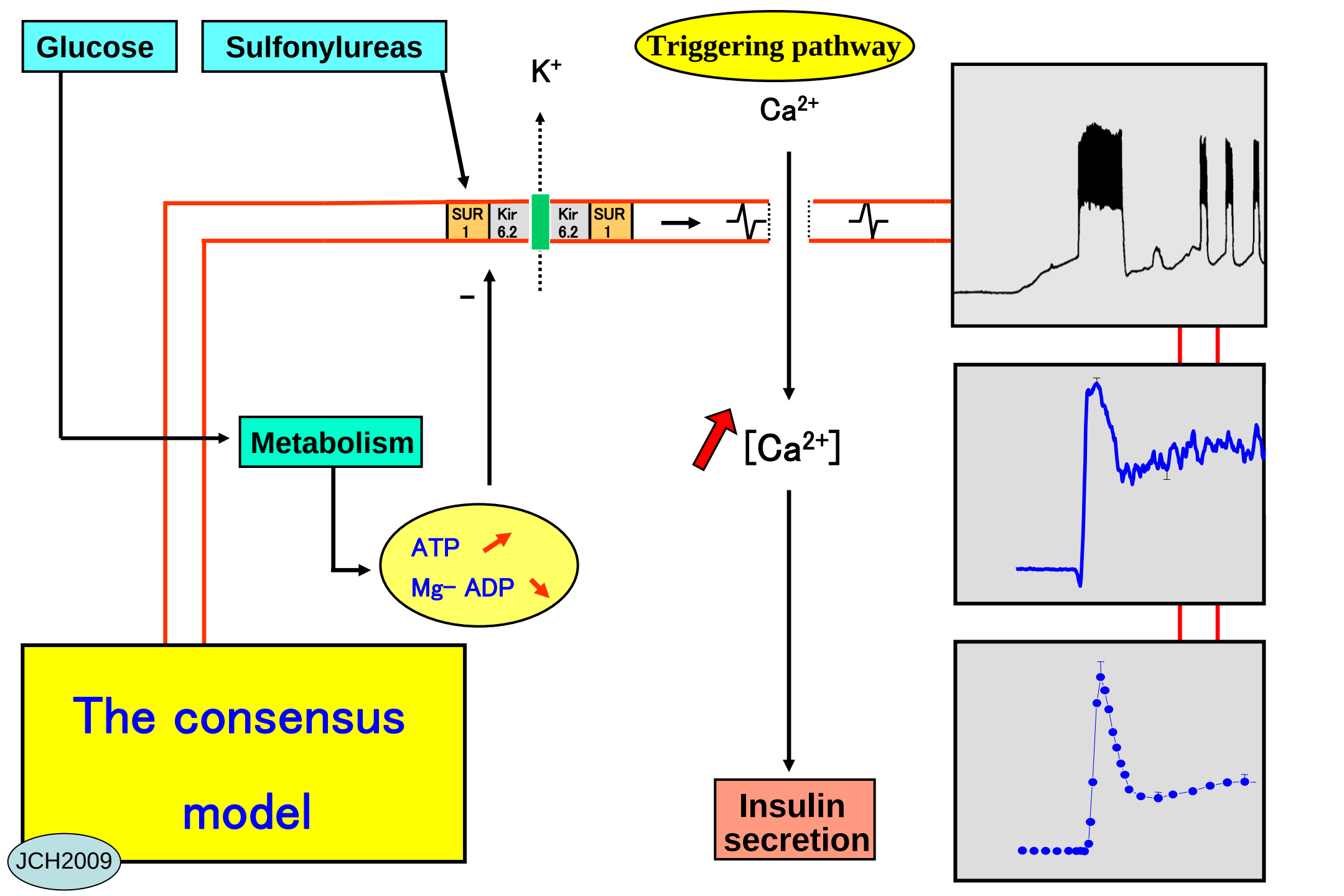
Glucose
Sulfonylureas
K+
Triggering pathway
Ca2+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
–
Metabolism
[Ca2+]
ATP
Mg– ADP
The consensus model
Insulin secretion
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Identification of shortcomings

in the consensus model of

glucose-induced insulin secretion

Discrepancy between triggering signal and insulin secretion

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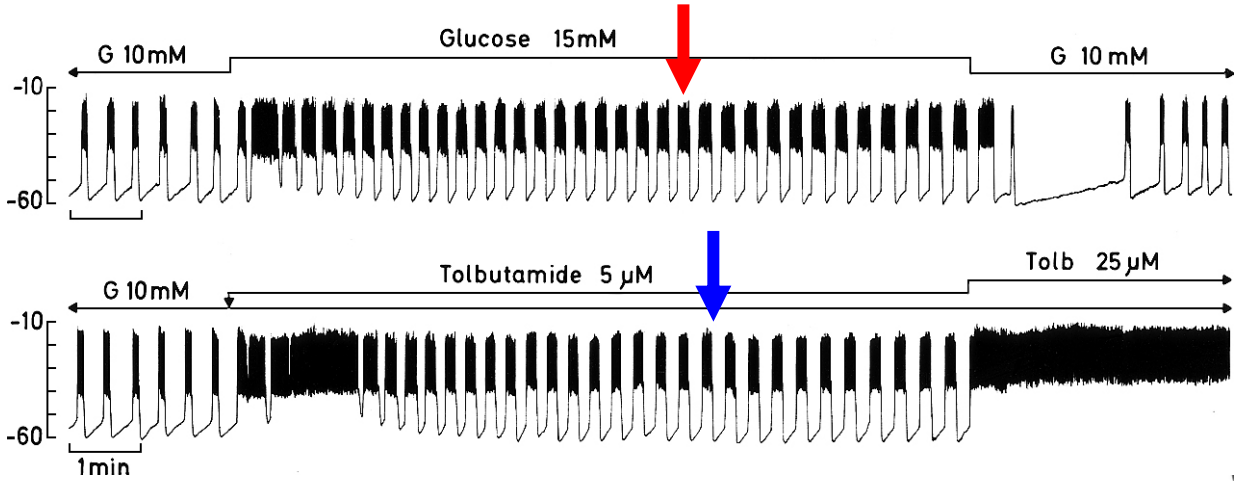
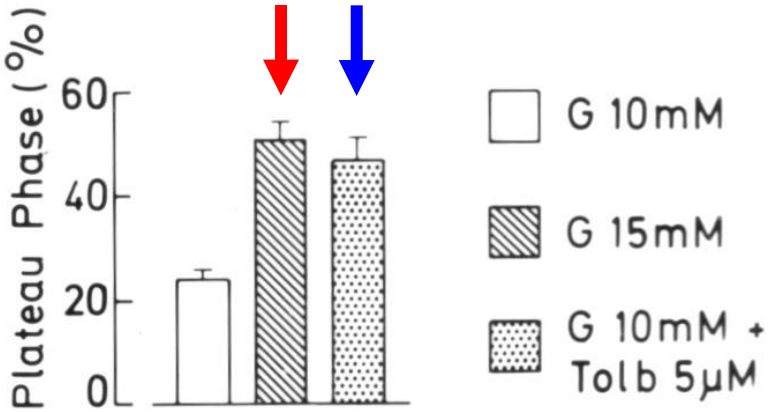
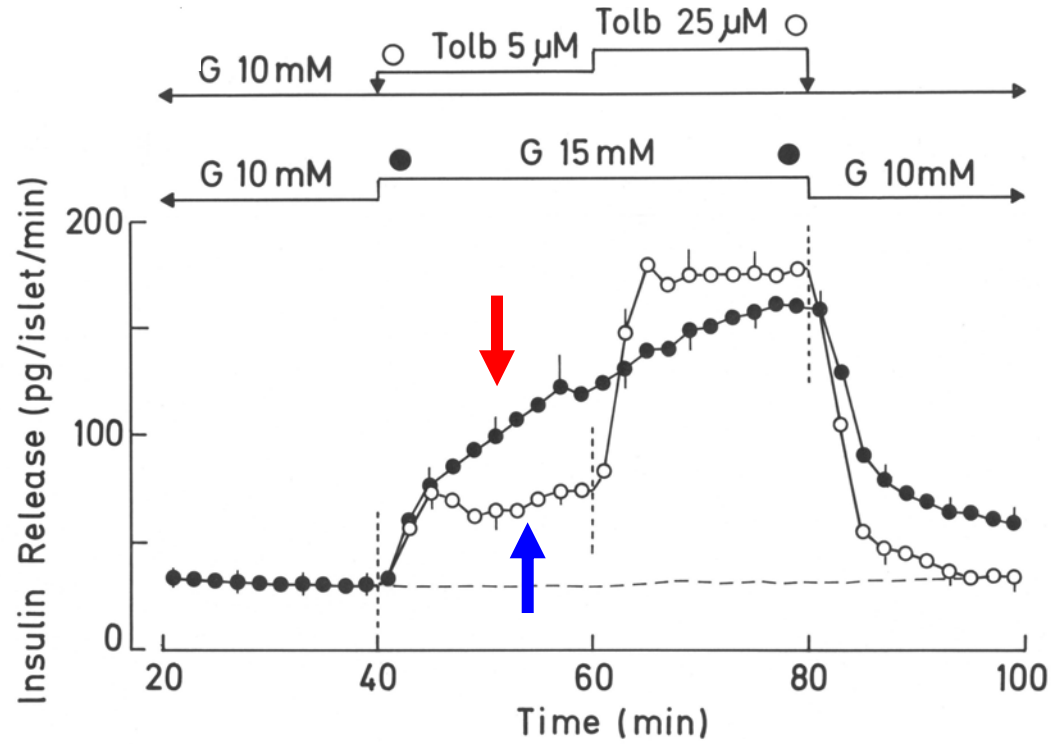
Electrical activity in a β-cell





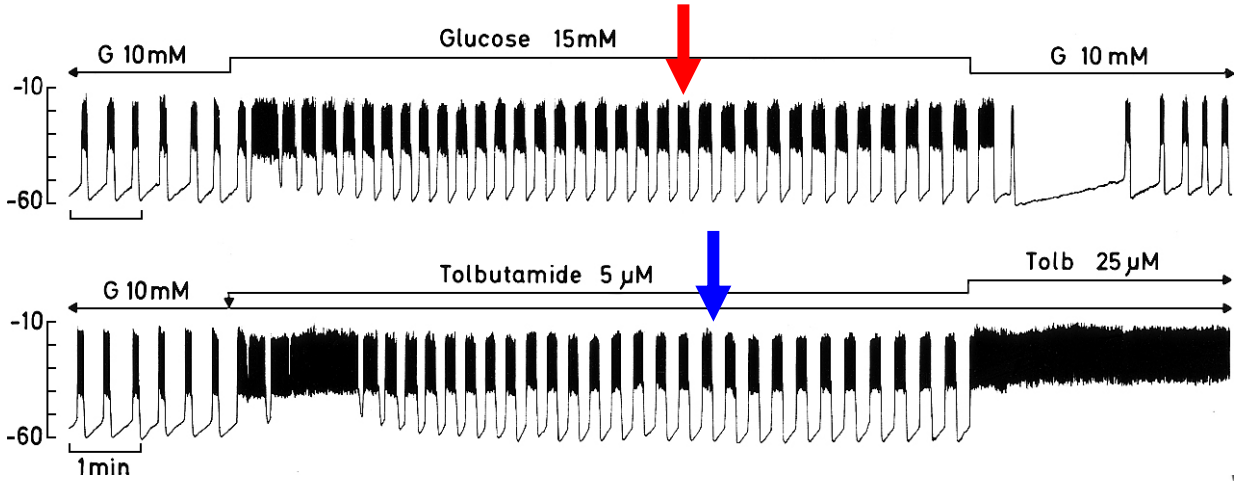
BBRC, 1988

Insulin secretion



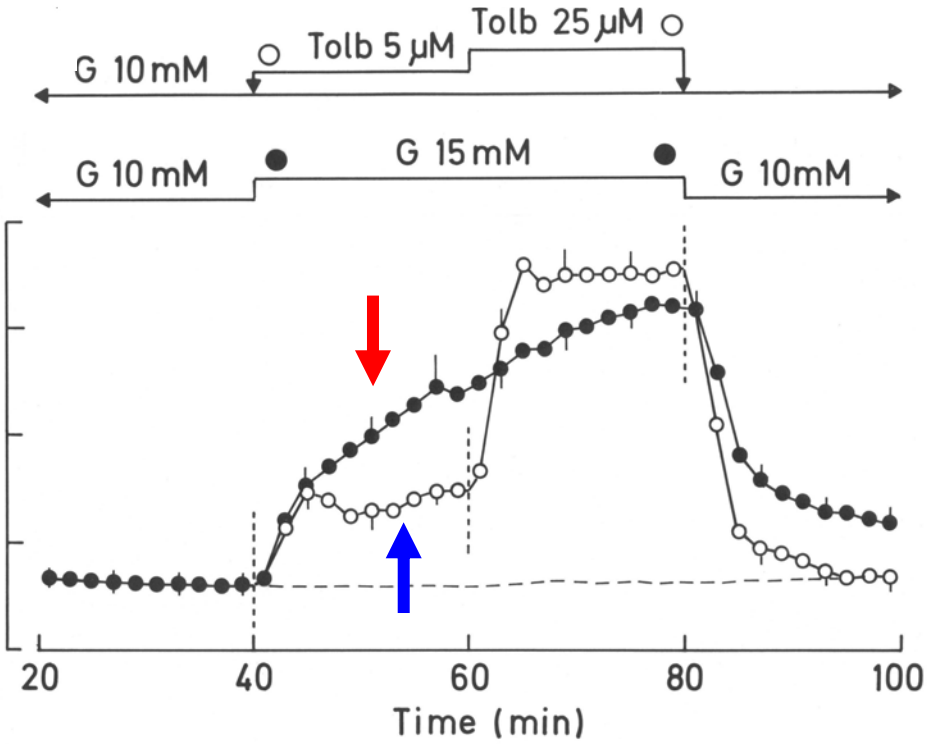
Discrepancy between triggering signal and insulin secretion

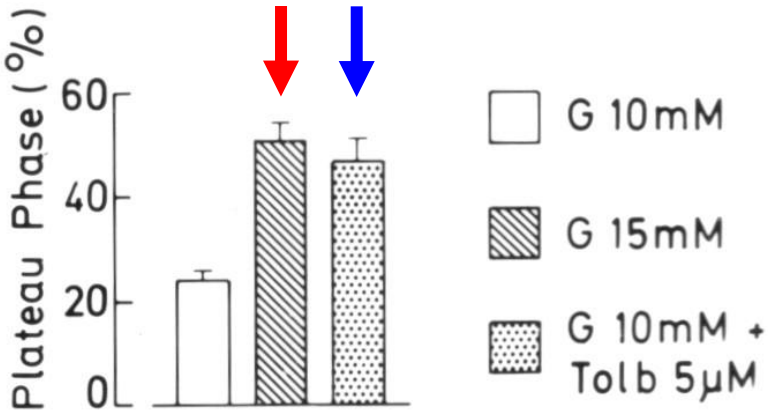
Electrical activity in a β-cell



"The results suggest that non-electrogenic effects of glucose amplify the release of insulin."

Insulin secretion





BBRC, 1988

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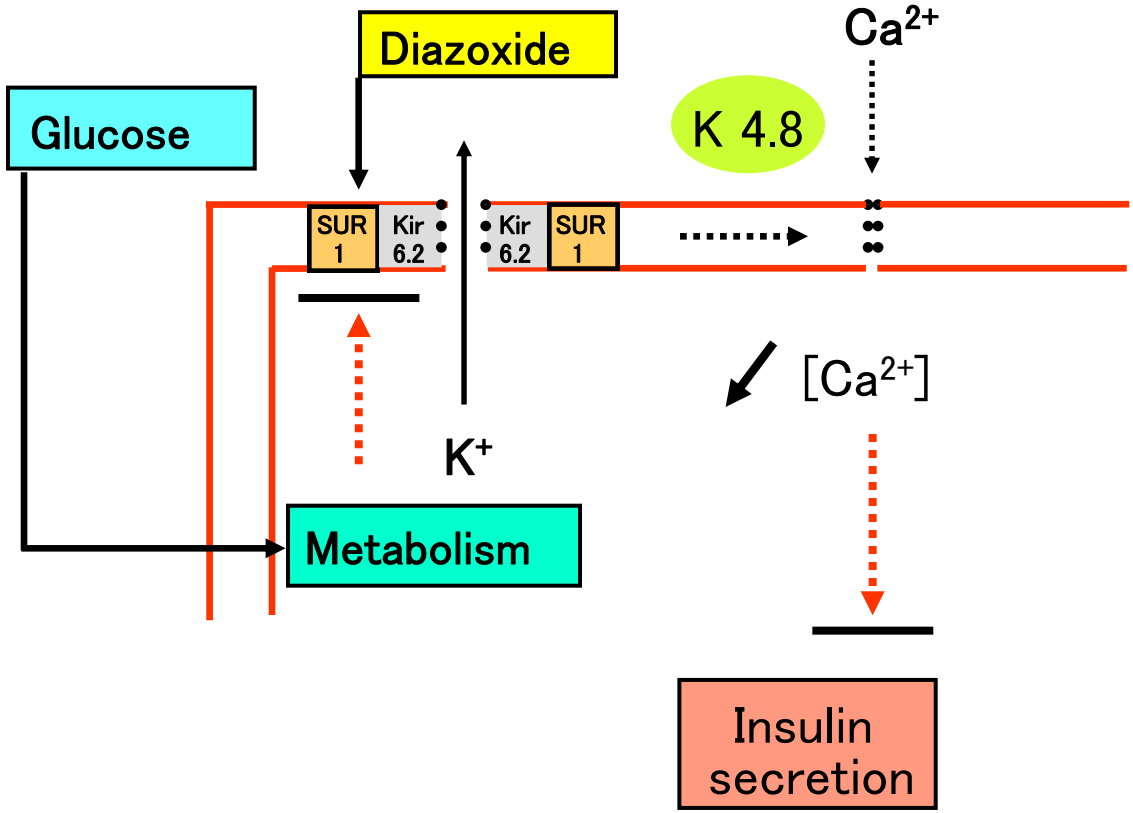
A K_{ATP} channel-independent effect of glucose on insulin secretion ?

K_{ATP} channels are held open by diazoxide a



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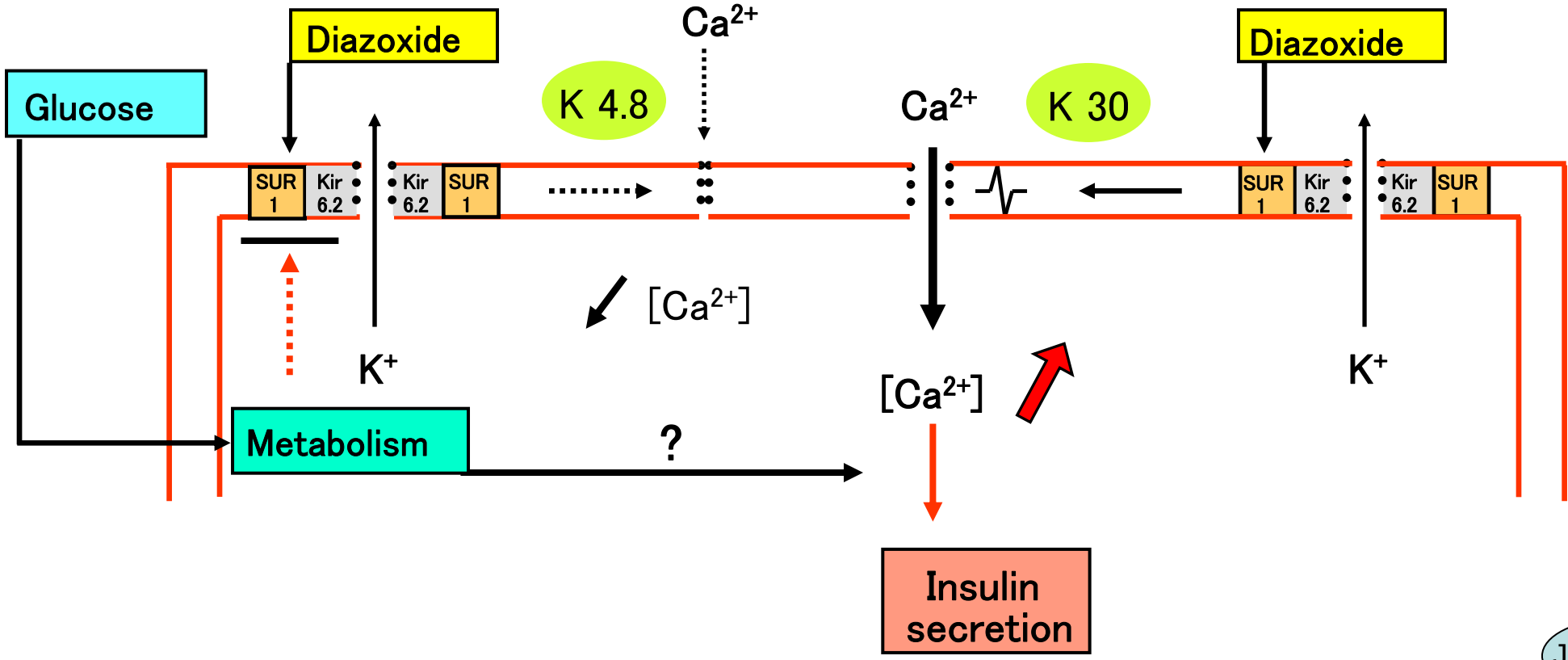
A K_{ATP} channel-independent effect of glucose on insulin secretion ?

K_{ATP} channels are held open by diazoxide and $[Ca^{2+}]_c$ is elevated with KCl



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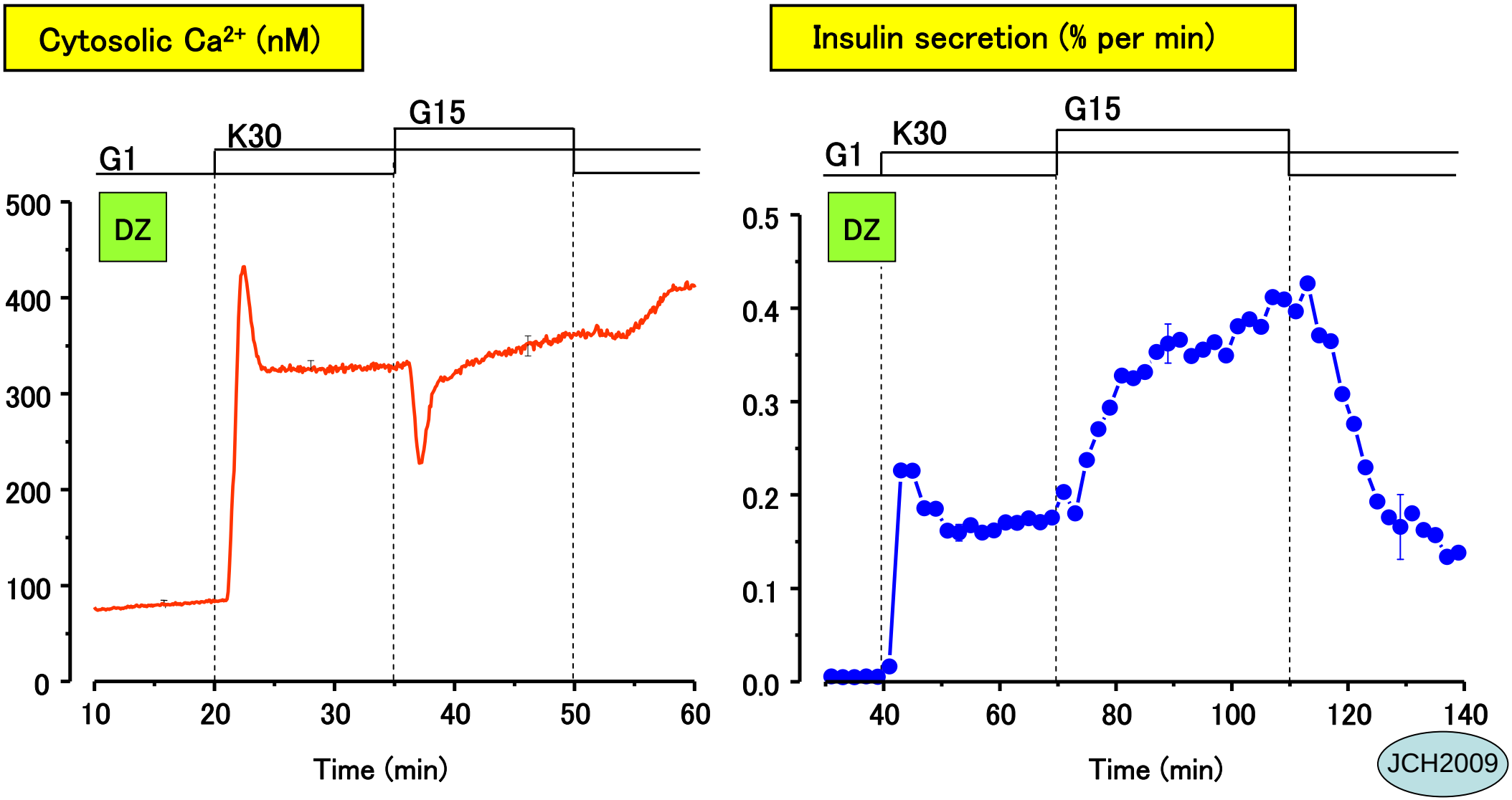

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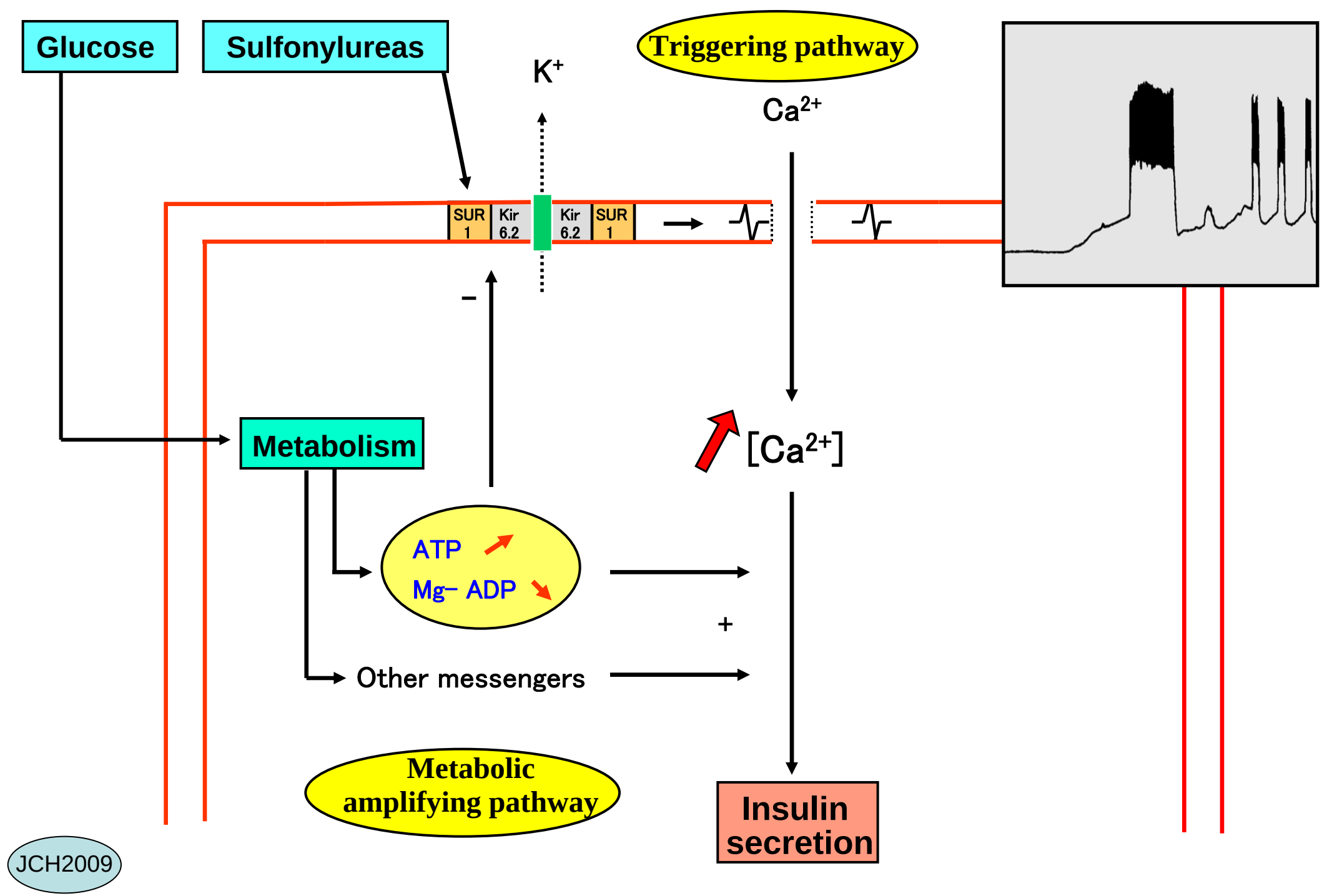
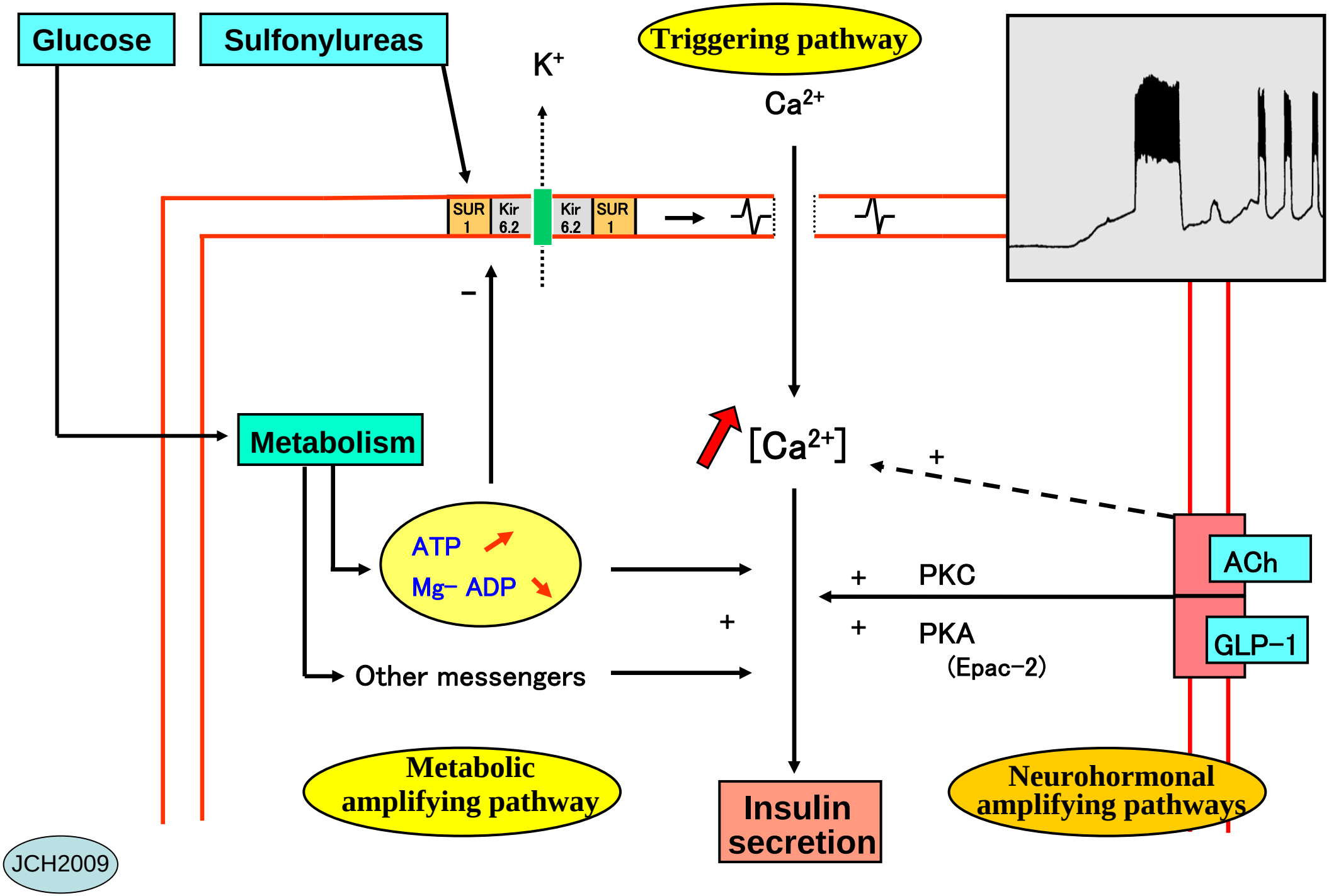

Glucose
Sulfonylureas
K+
Triggering pathway
Ca2+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
–
Metabolism
[Ca2+]
ATP
Mg– ADP
+
Other messengers
Metabolic amplifying pathway
Insulin secretion
JCH2009


Glucose
Sulfonylureas
K+
Triggering pathway
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SUR 1
Kir 6.2
Kir 6.2
SUR 1
−
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+
ATP
Mg− ADP
+
PKC
+
PKA
(Epac−2)
ACh
GLP−1
Other messengers
Metabolic amplifying pathway
Insulin secretion
Neurohormonal amplifying pathways
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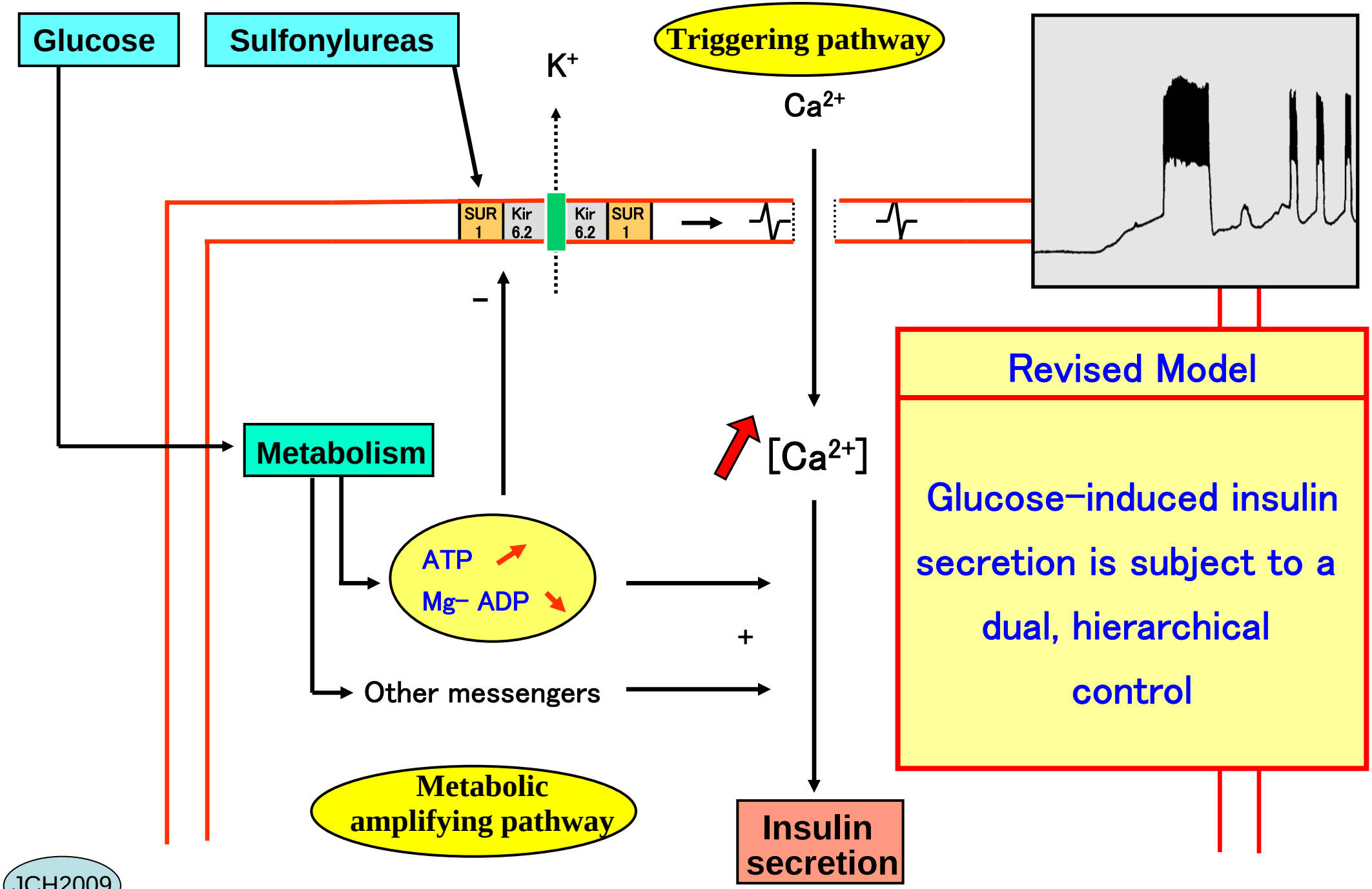
Glucose
Sulfonylureas
K+
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Kir 6.2
SUR 1
Revised Model
Glucose-induced insulin secretion is subject to a dual, hierarchical control
–
Metabolism
[Ca2+]
ATP
Mg- ADP
+
Other messengers
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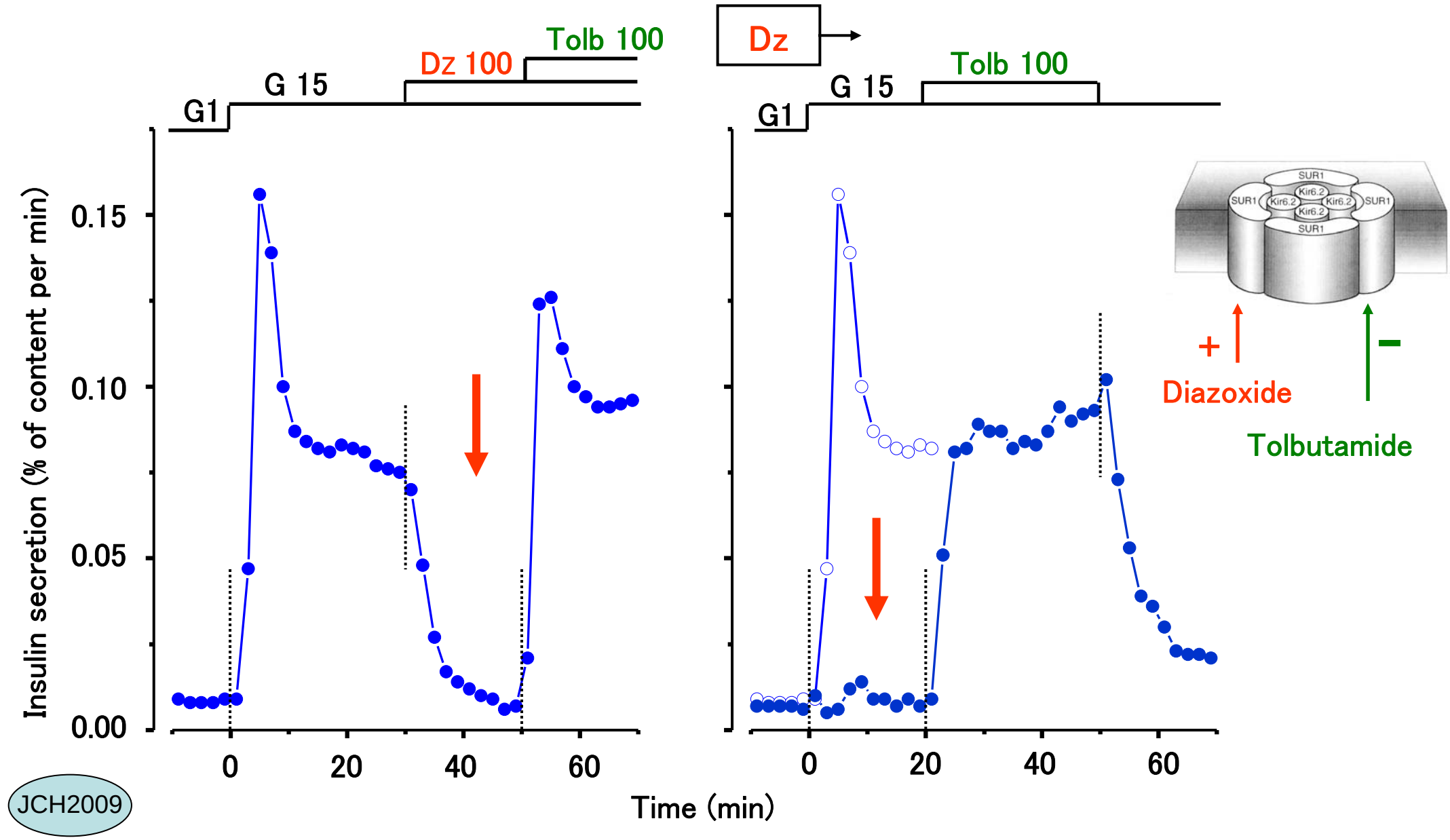
Insulin secretion
JCH2009

The triggering pathway is essential for both phases of GSIS



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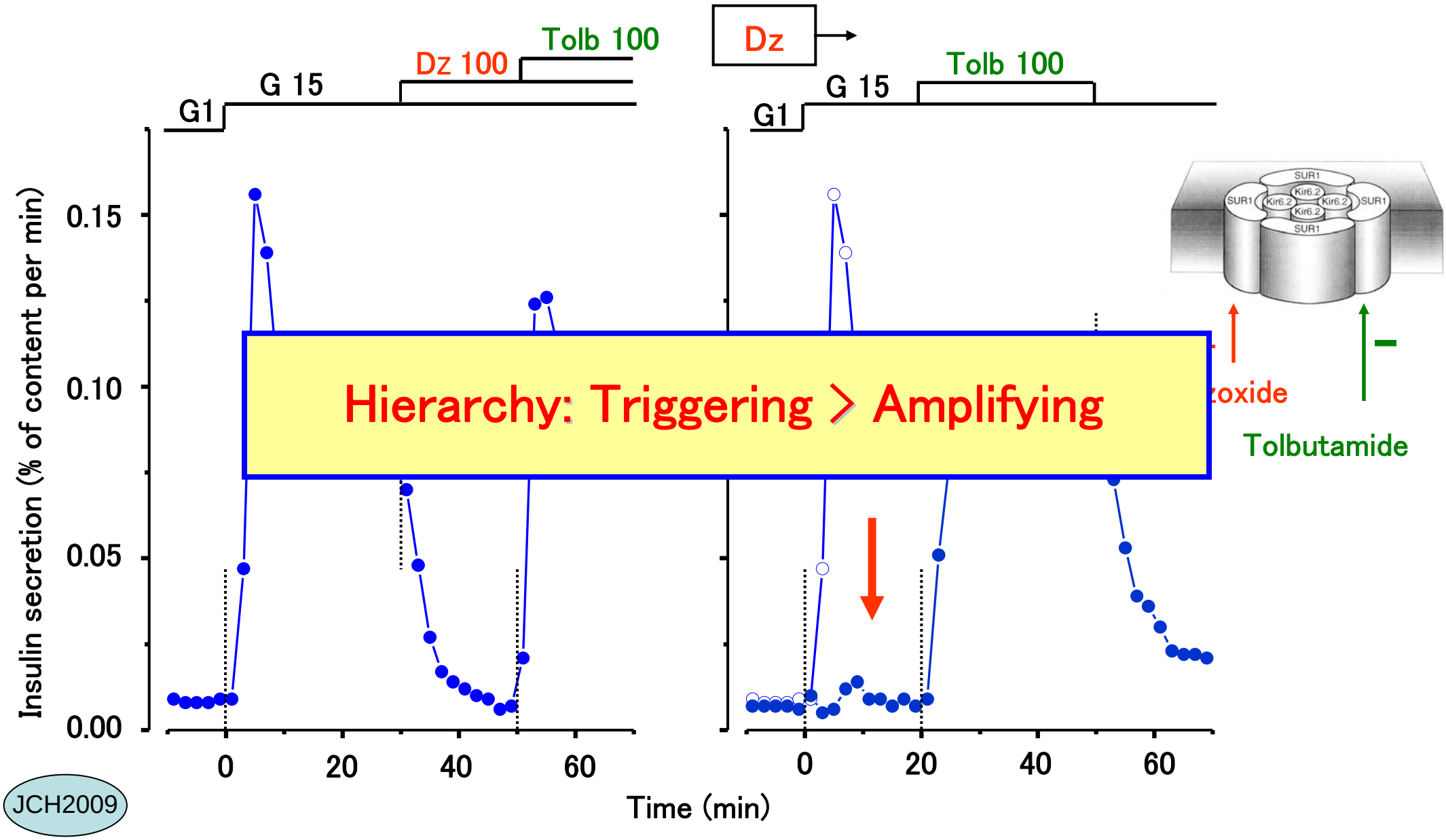

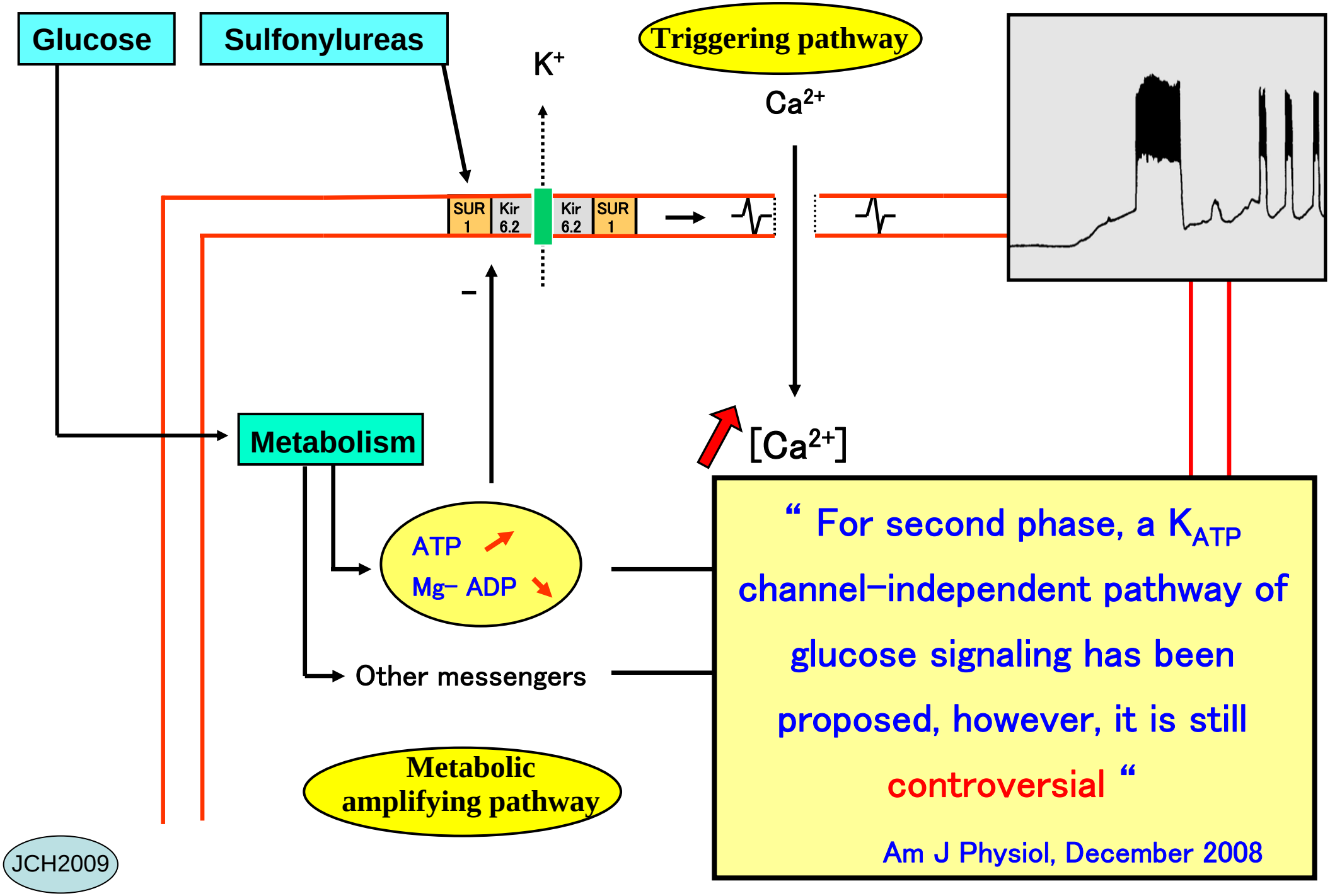
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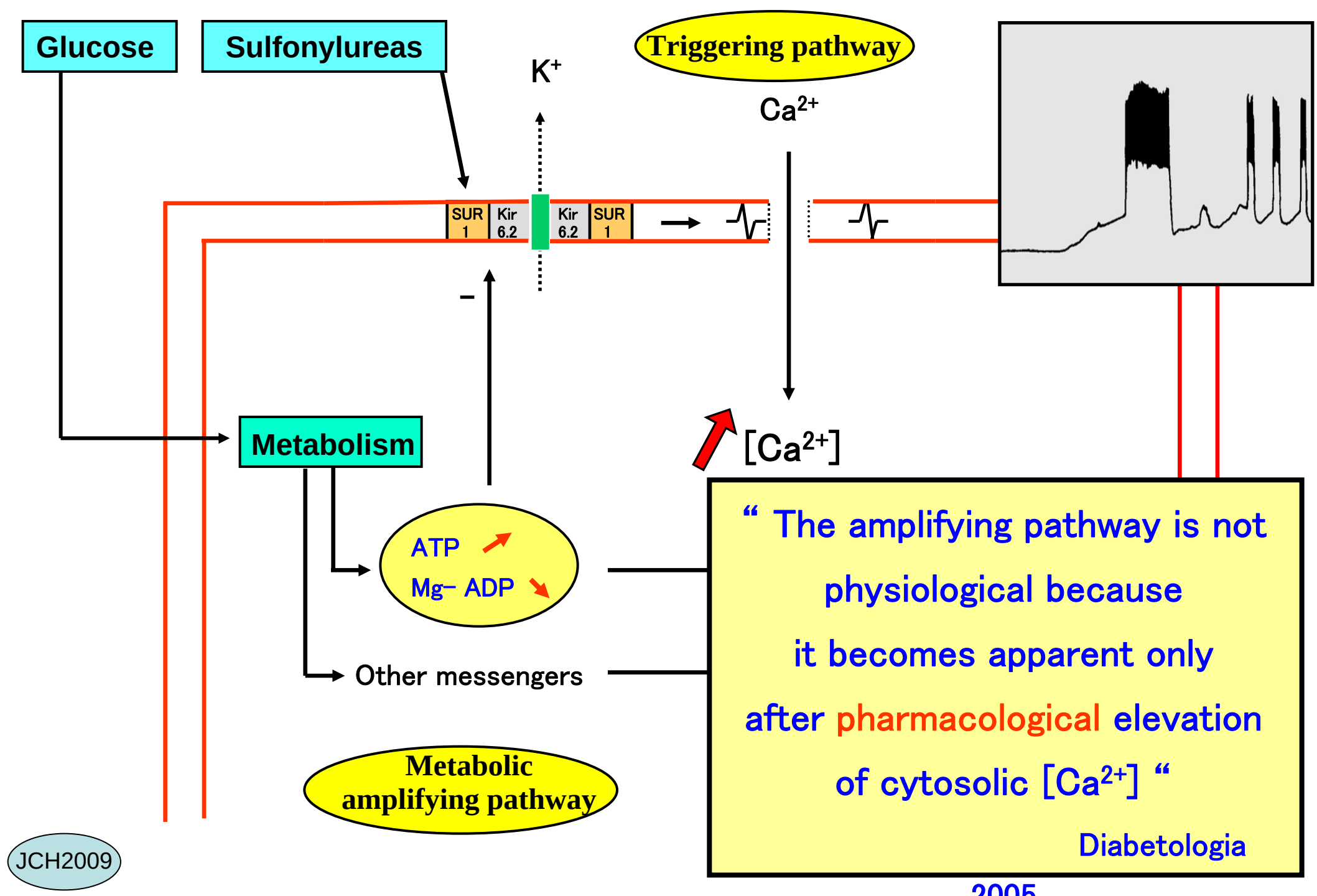
[Ca2+]
ATP
Mg– ADP
Other messengers
Metabolic amplifying pathway
" For second phase, a K_{ATP} channel–independent pathway of glucose signaling has been proposed, however, it is still controversial "
Am J Physiol, December 2008
JCH2009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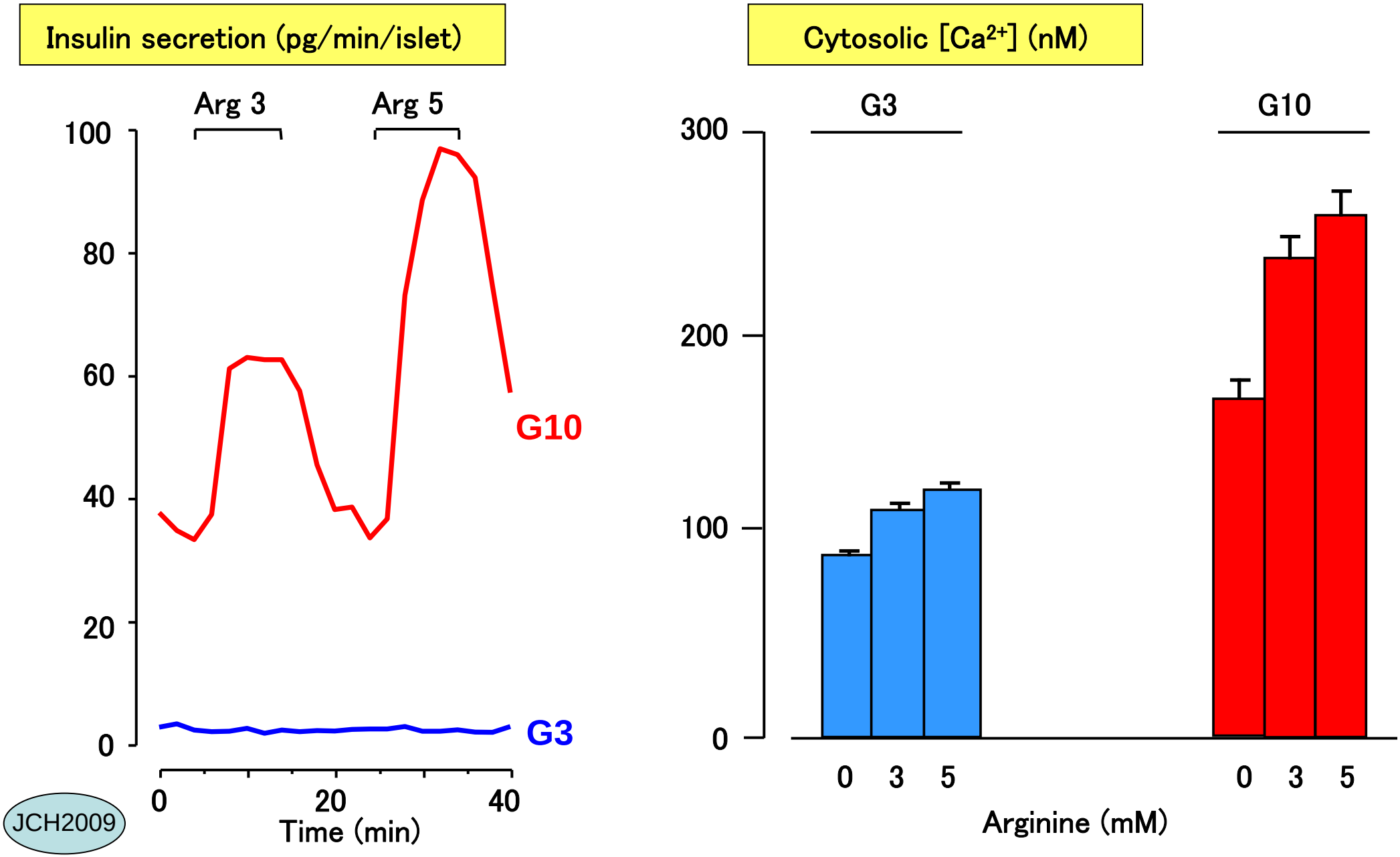
[Ca2+]
ATP
Mg– ADP
Other messengers
Metabolic amplifying pathway
“ The amplifying pathway is not physiological because it becomes apparent only after pharmacological elevation of cytosolic [Ca2+] “
Diabetologia
2005
JCH2009

The amplifying pathway during arginine-induced insulin secretion



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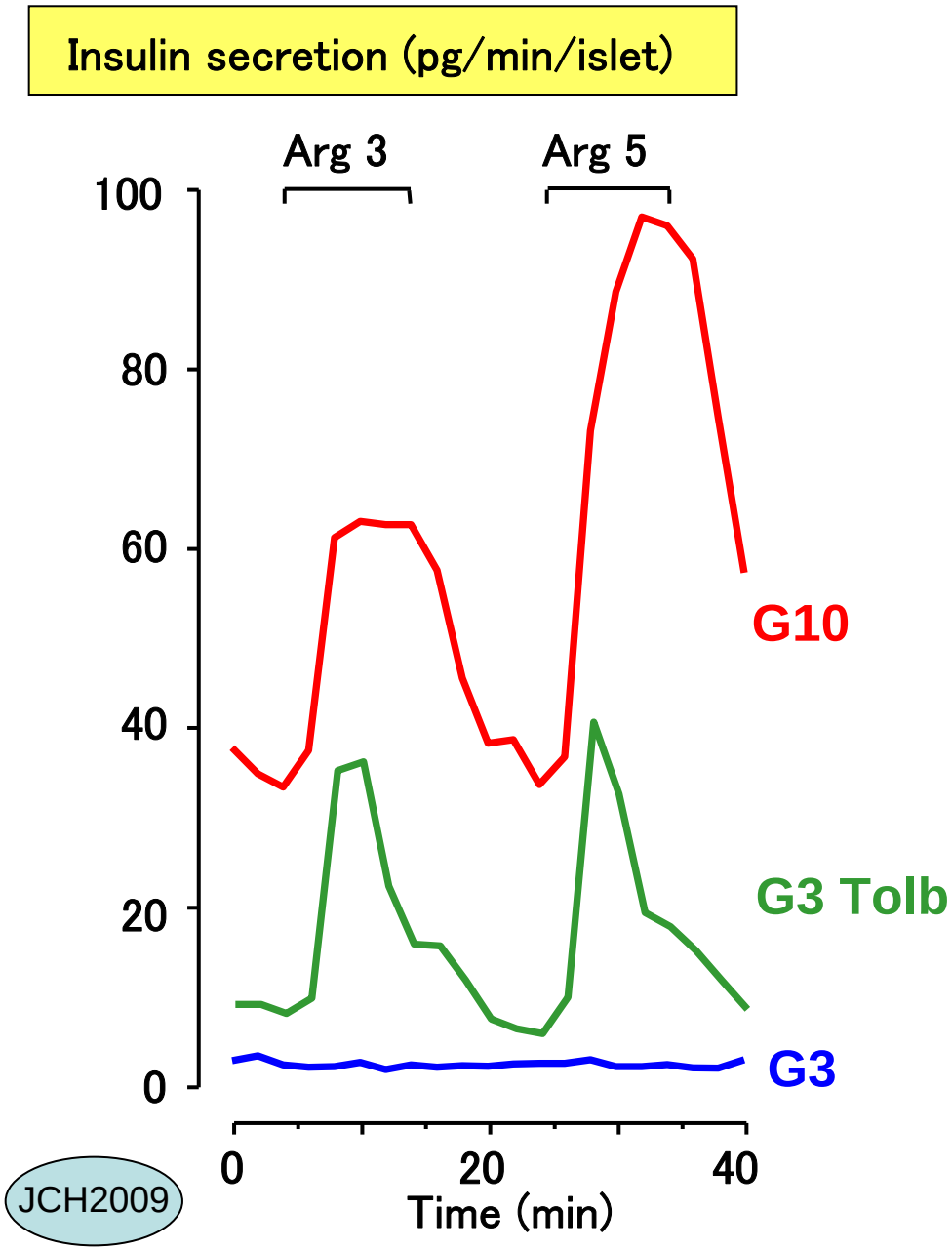

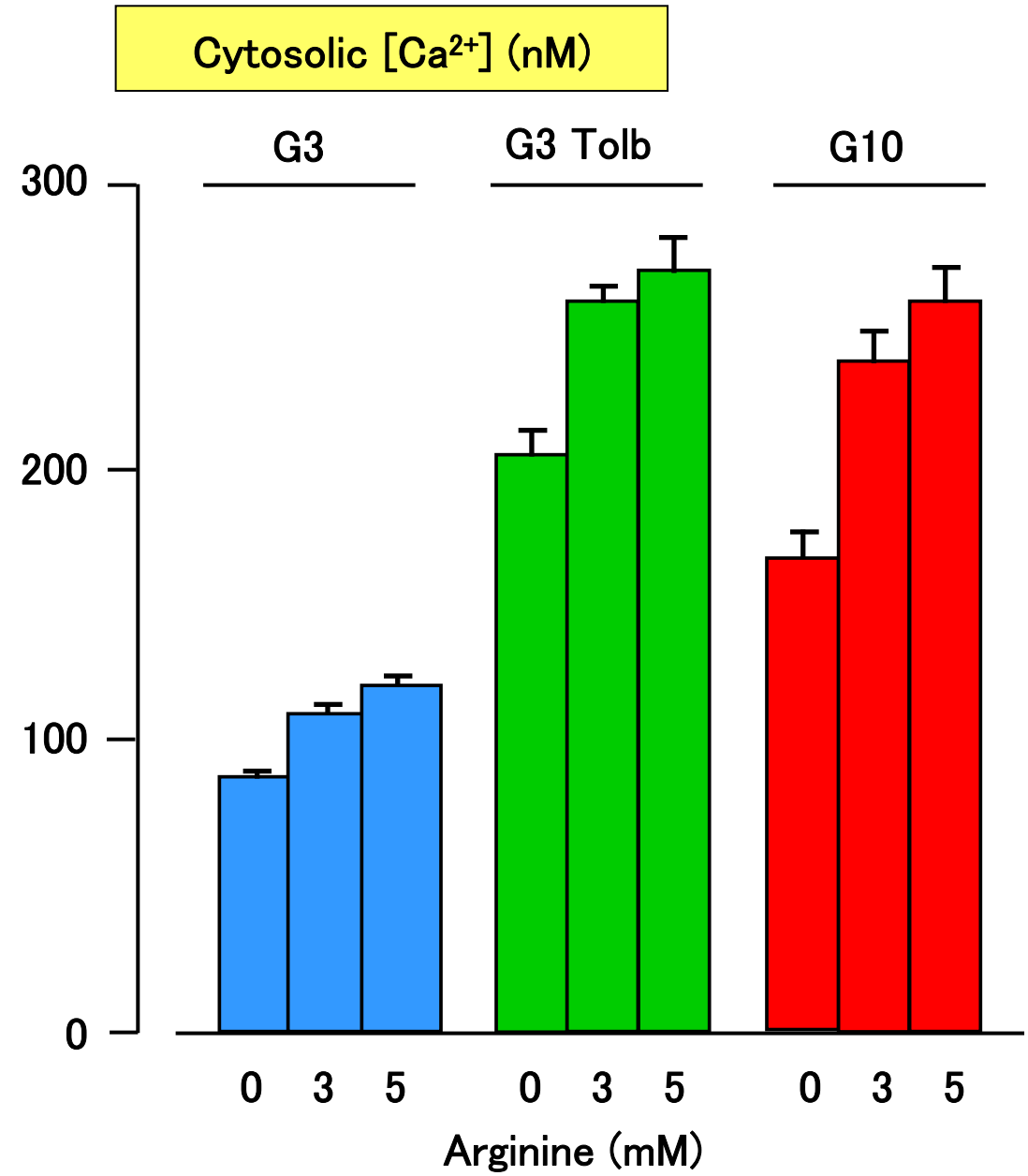

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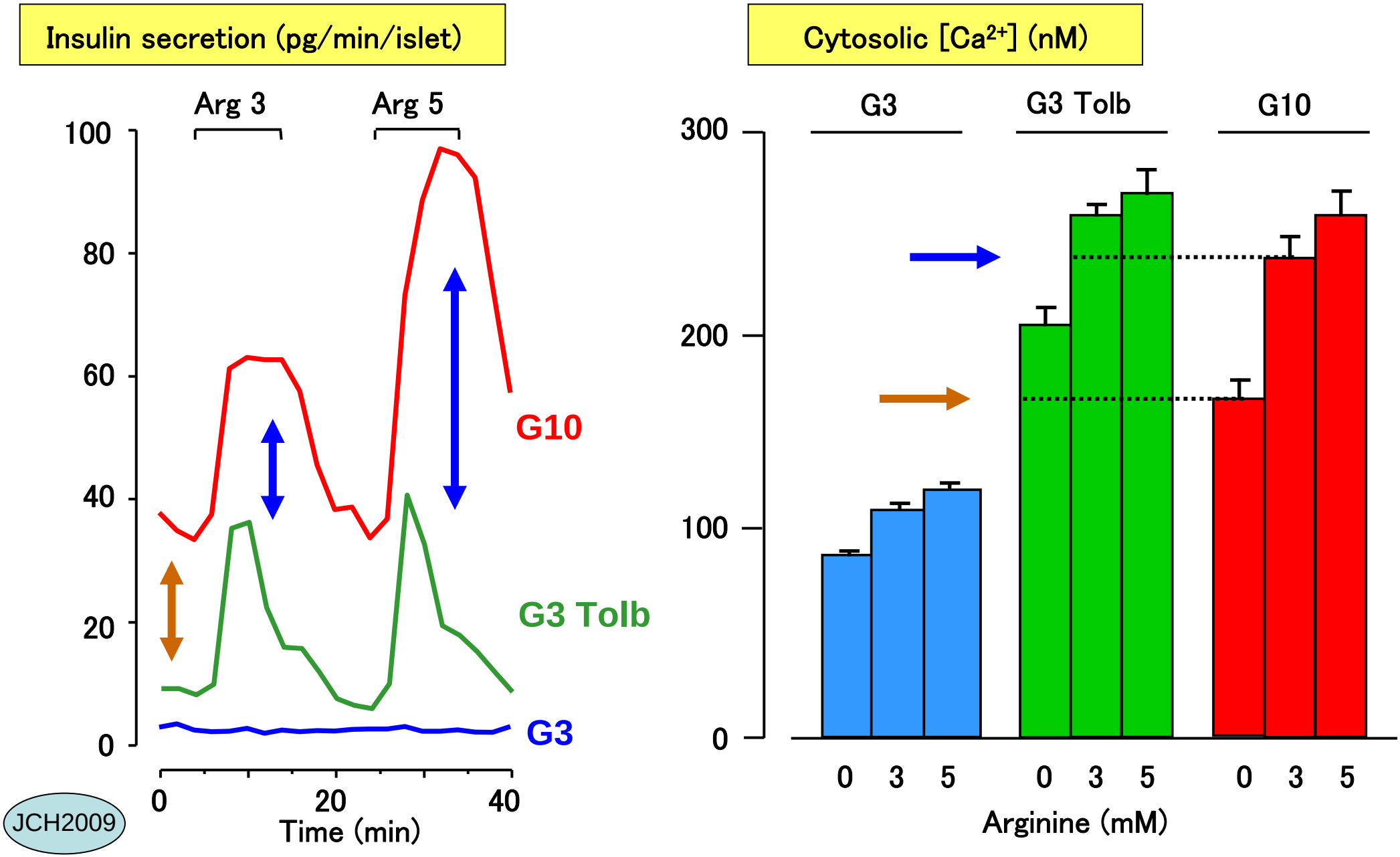
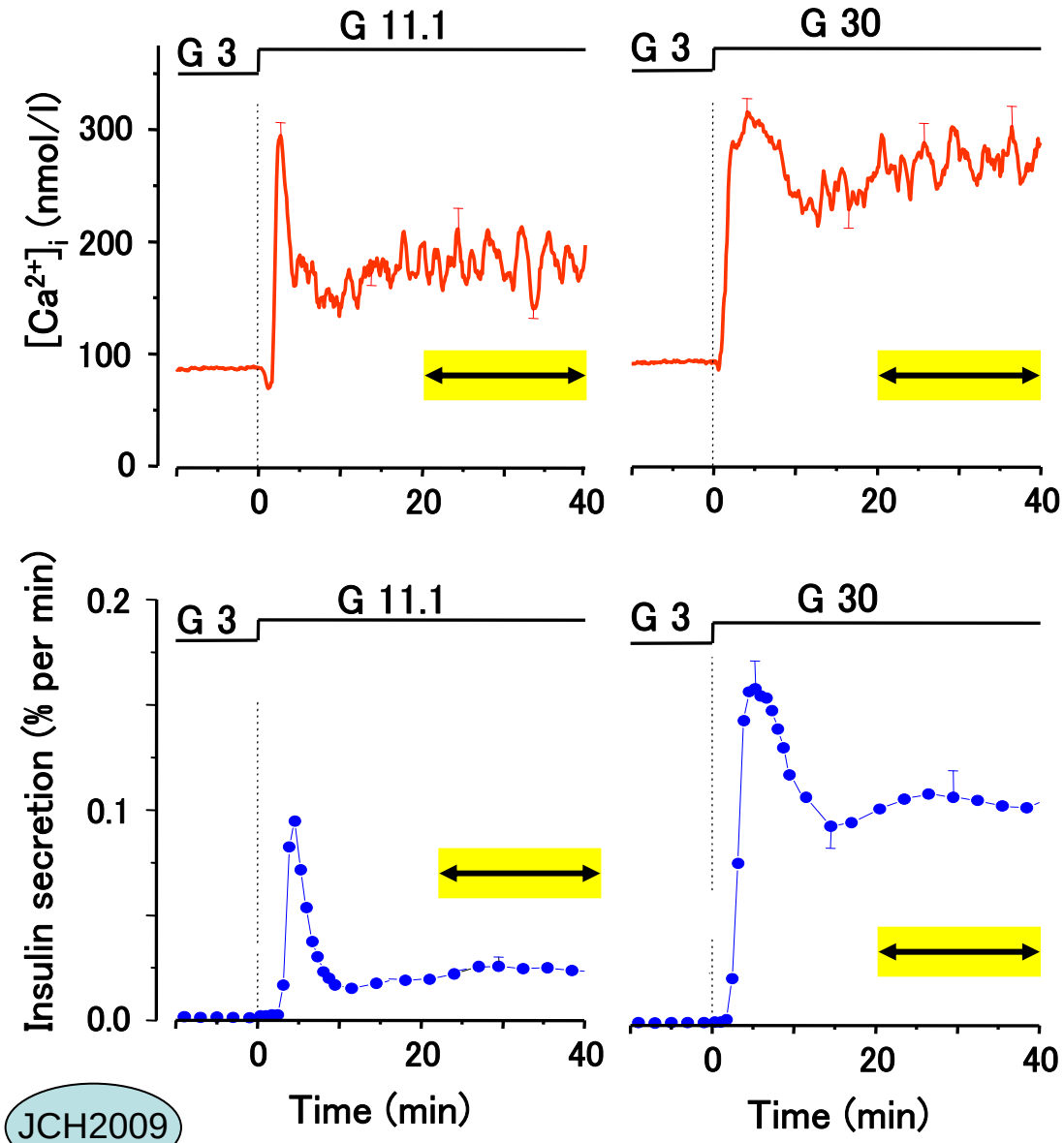


Triggering and amplifying pathways in second phase GSIS



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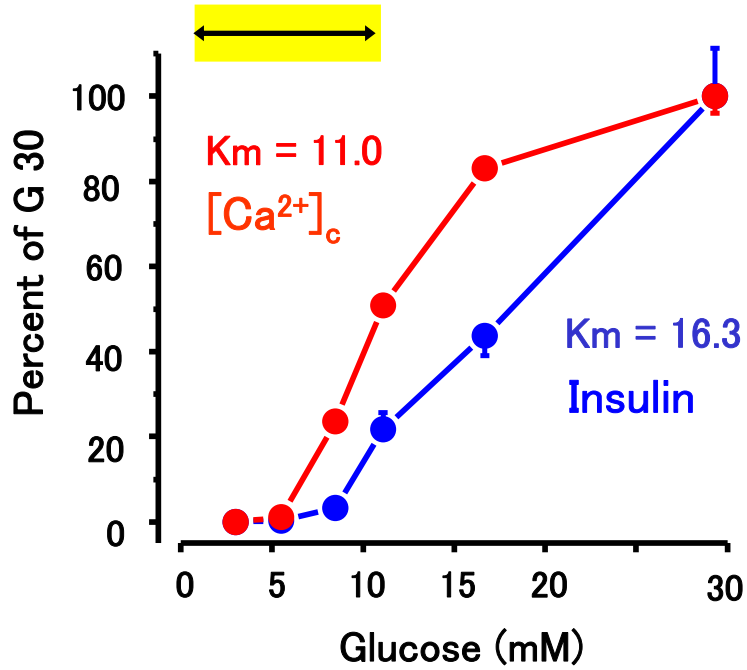


Dual control of glucose-induced insulin secretion by triggering and amplifying signals:

- clear for amplitude modulation

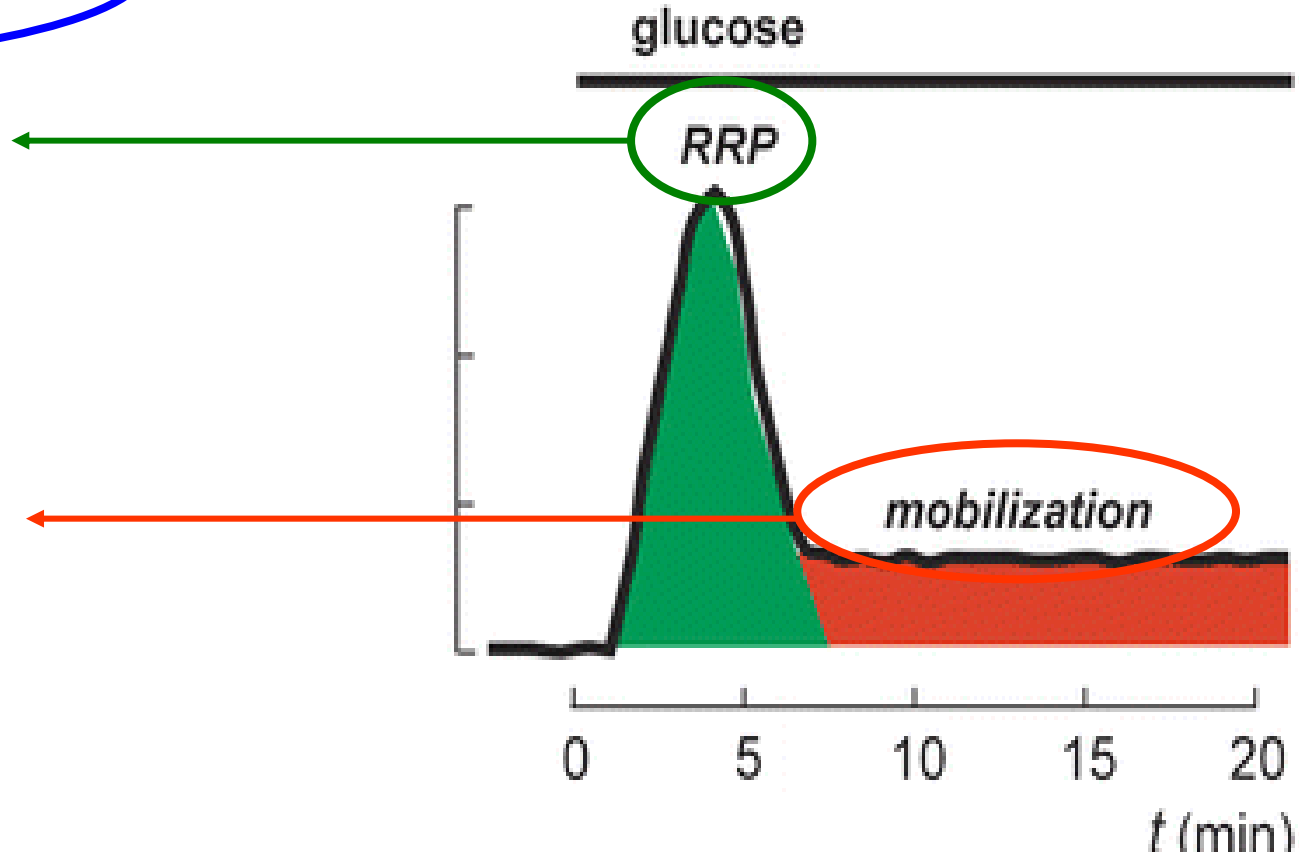
- also for time control (biphasic and pulsatile secretion)?

Two pathways and two phases of GSIS: what is the link?

Pools of insulin granules

Readily releasable (docked and primed)

Reserve (docked or not)



Rorsman and Renström, Diabetologia 2003

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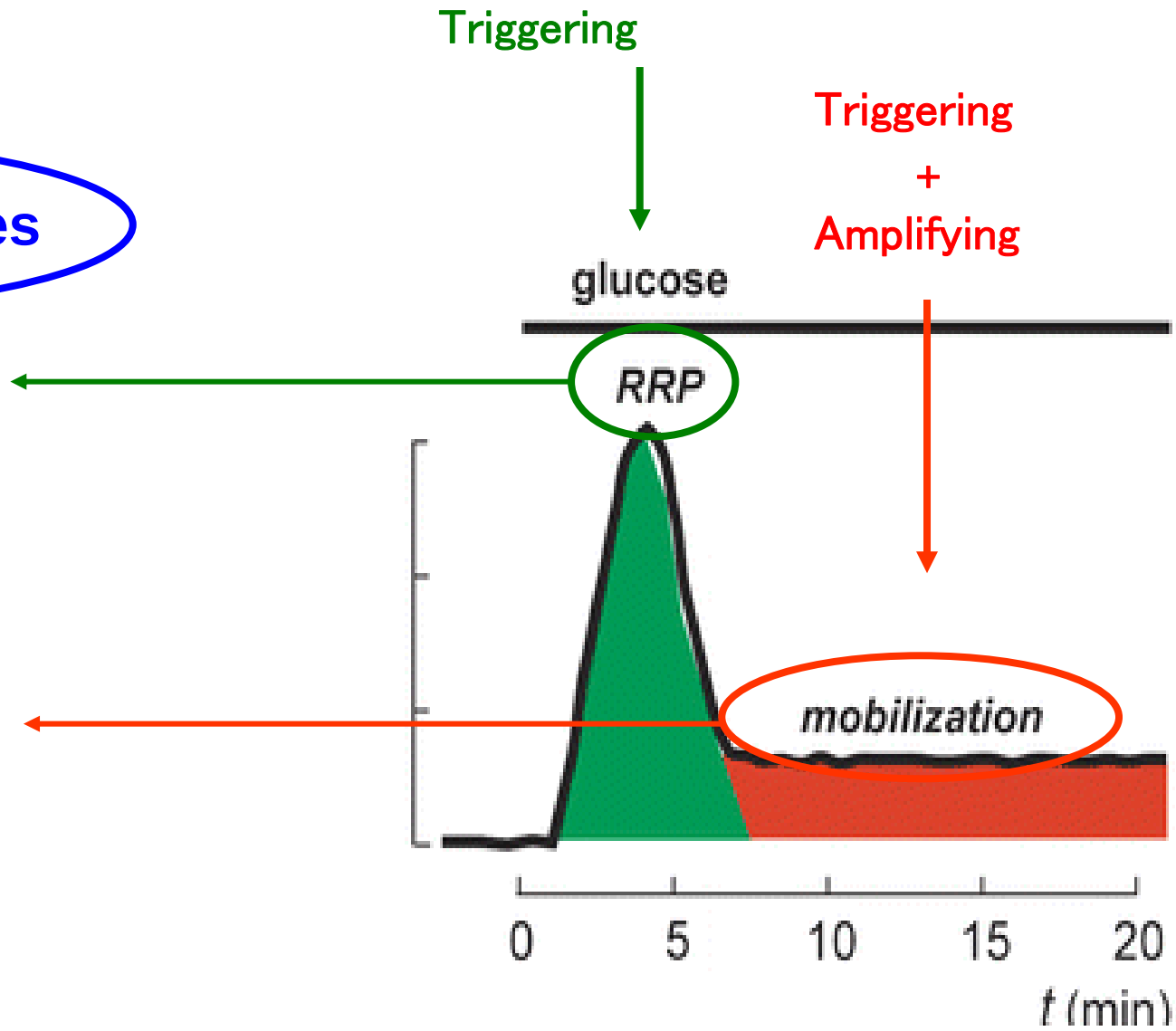

Rorsman and Renström, Diabetologia 2003

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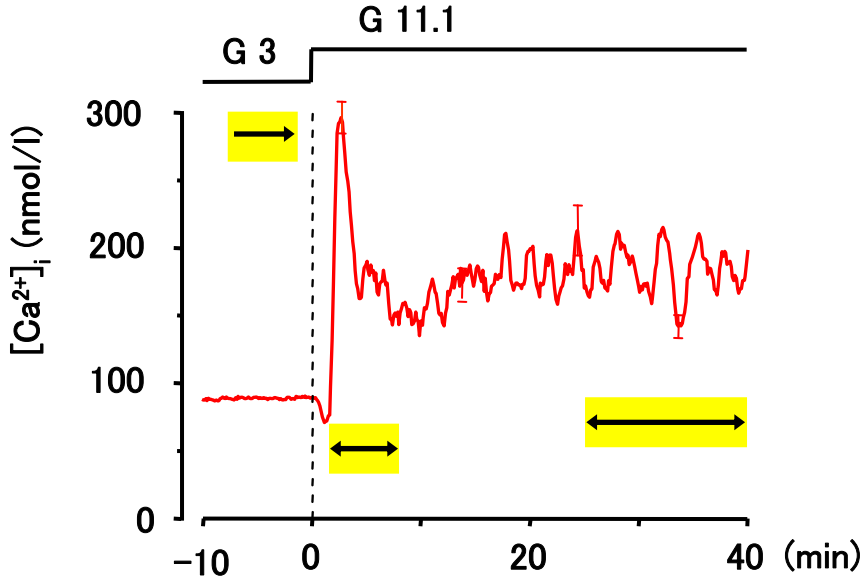
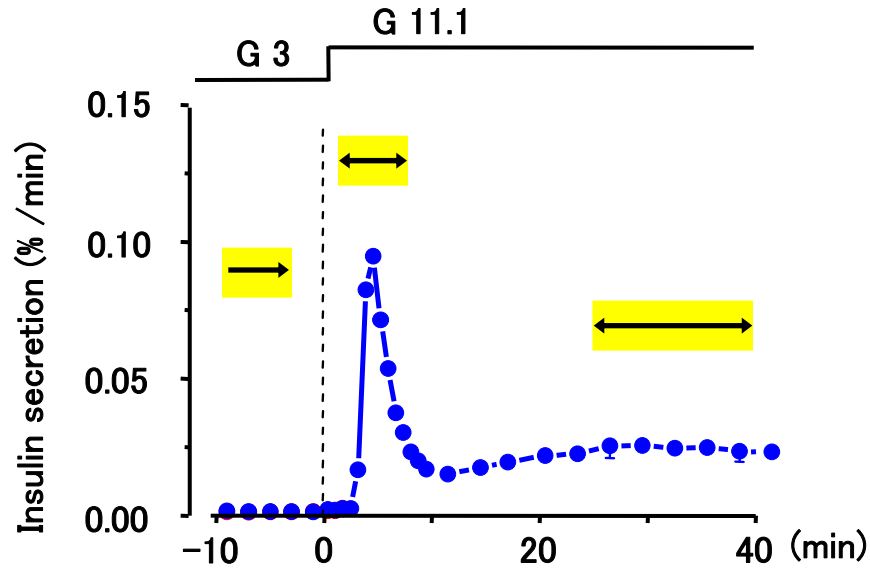
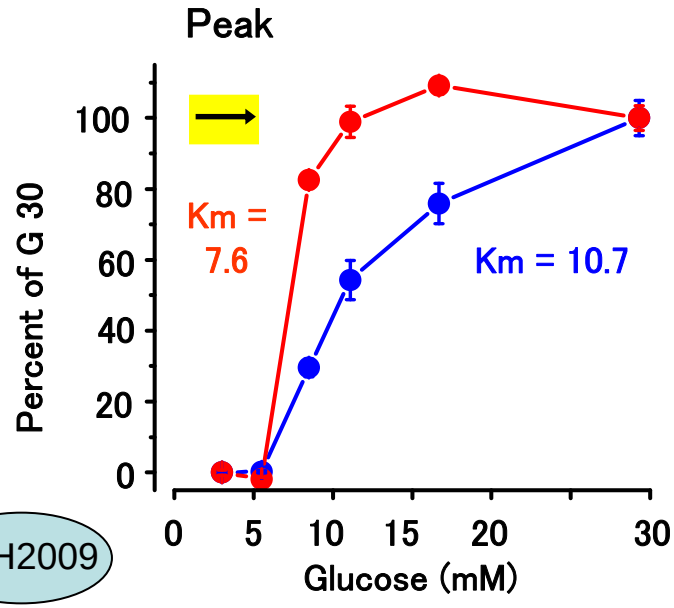
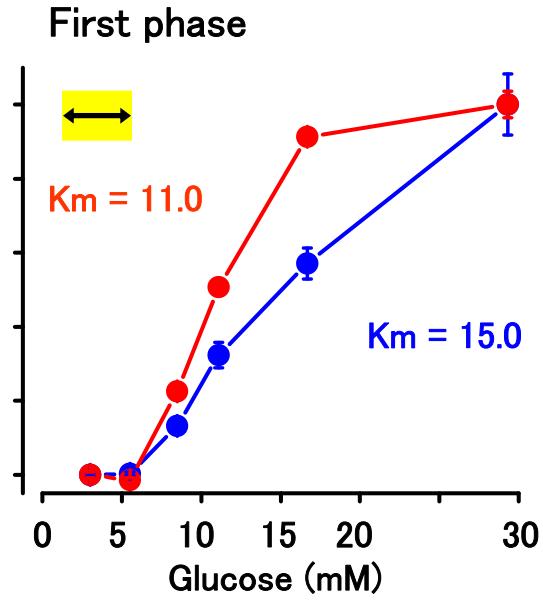
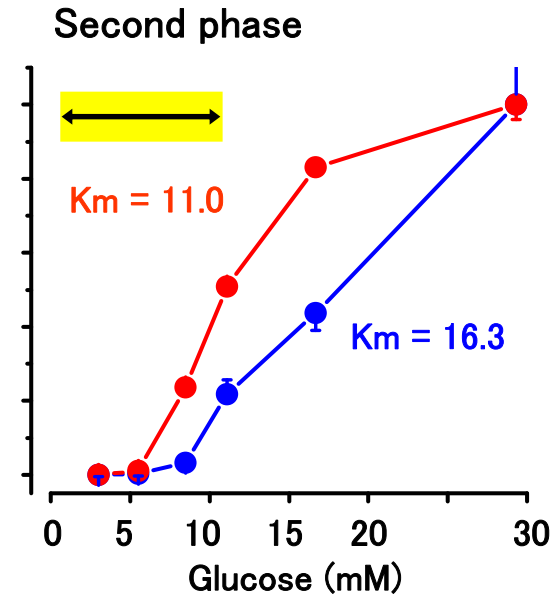
Triggering and amplifying pathways in biphasic GSIS











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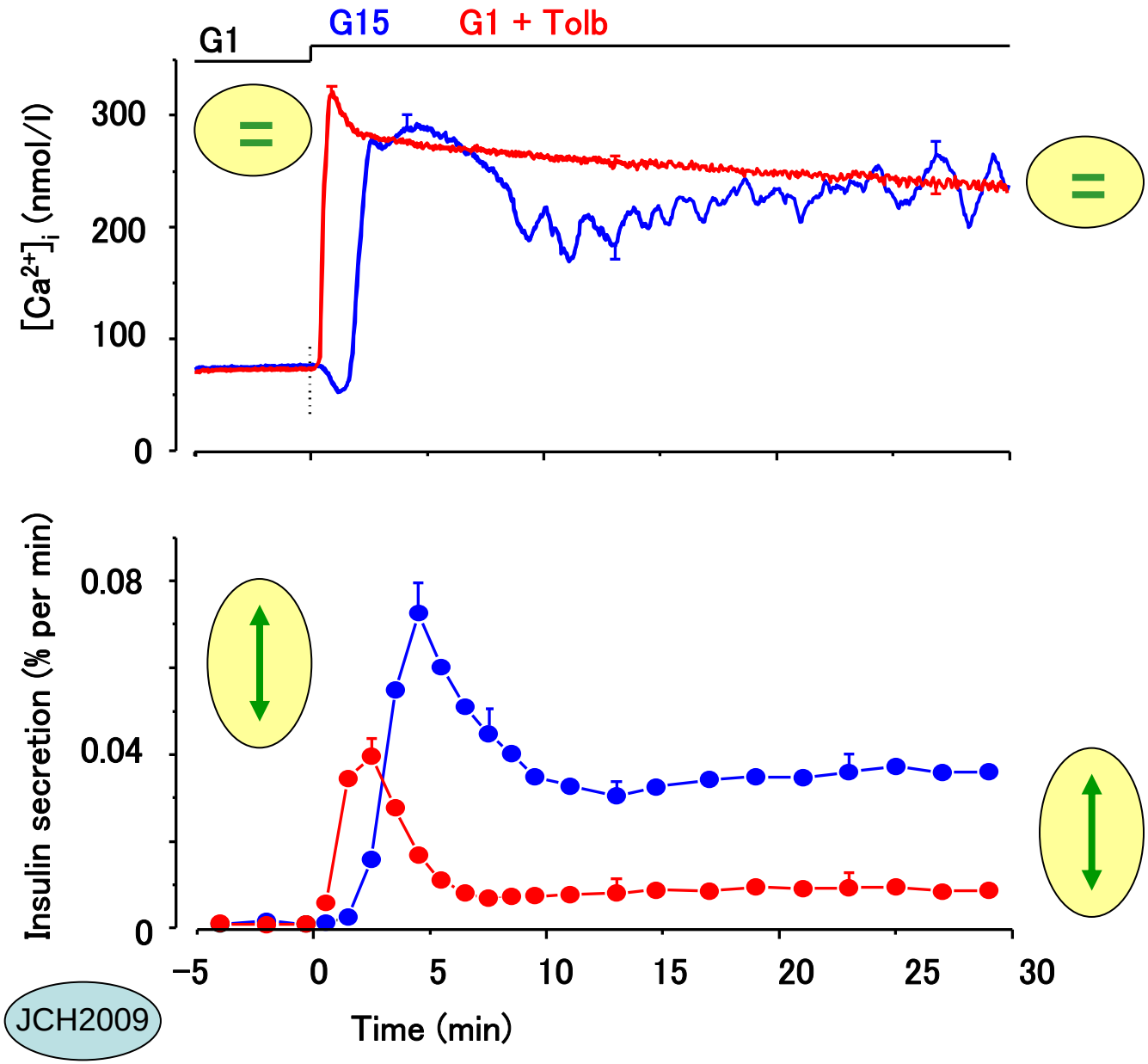
Triggering and amplifying pathways in biphasic GSIS



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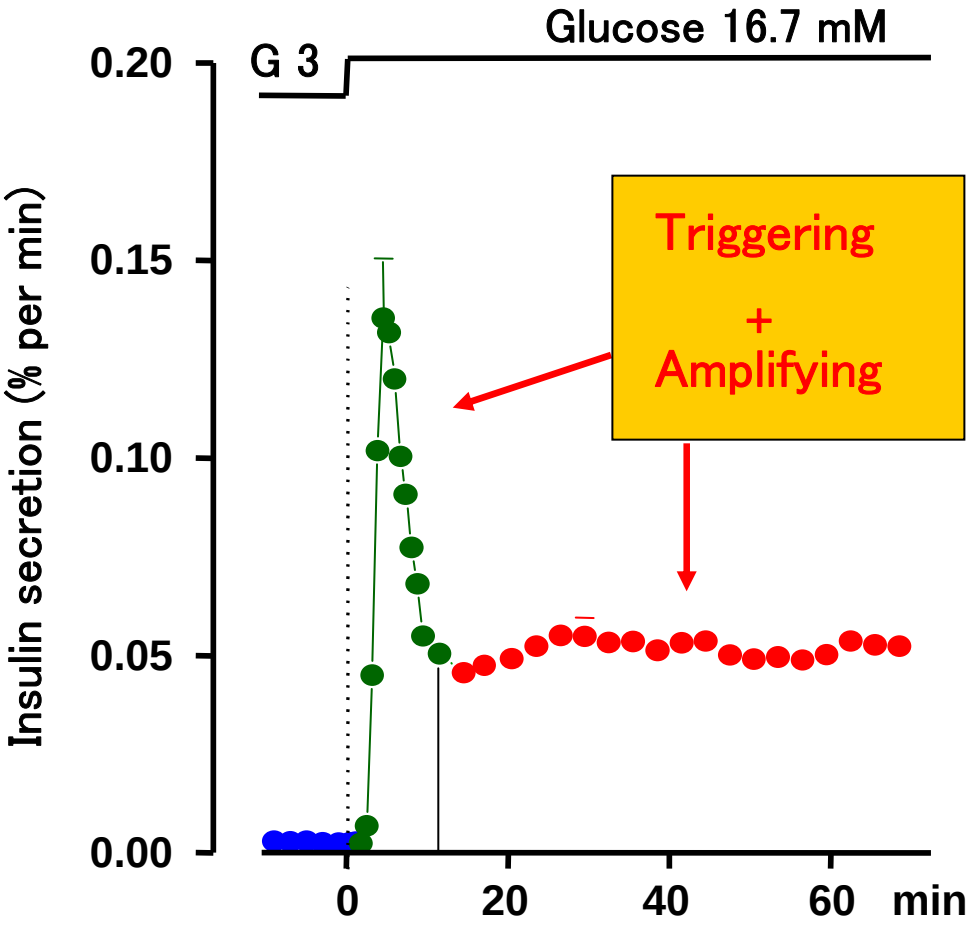
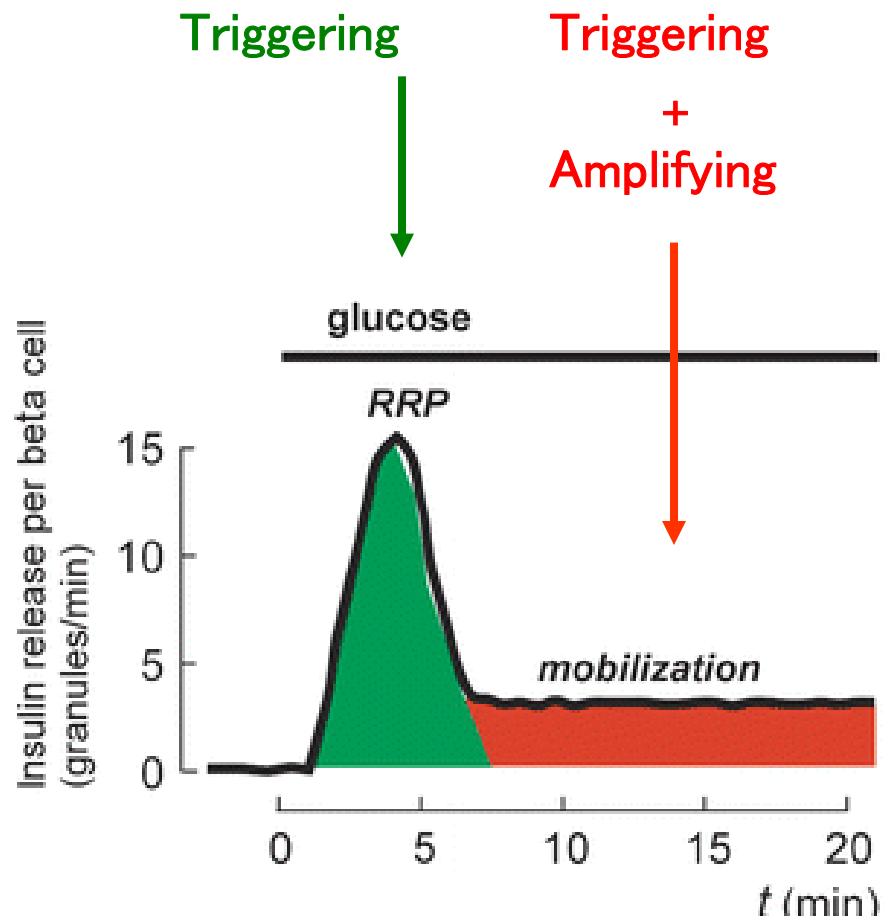
Biphasic insulin secretion: what about the two-pool model ?

NO !





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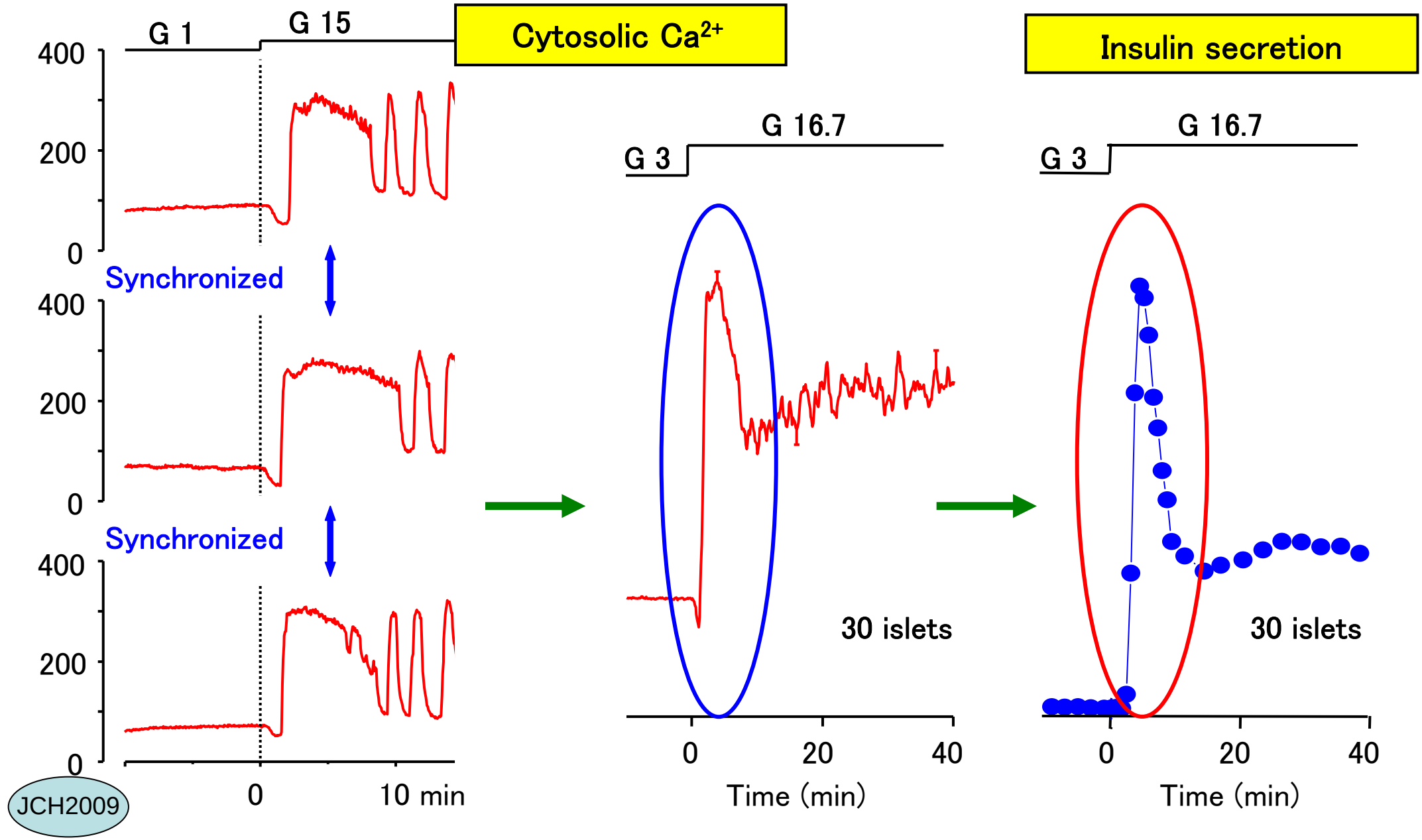
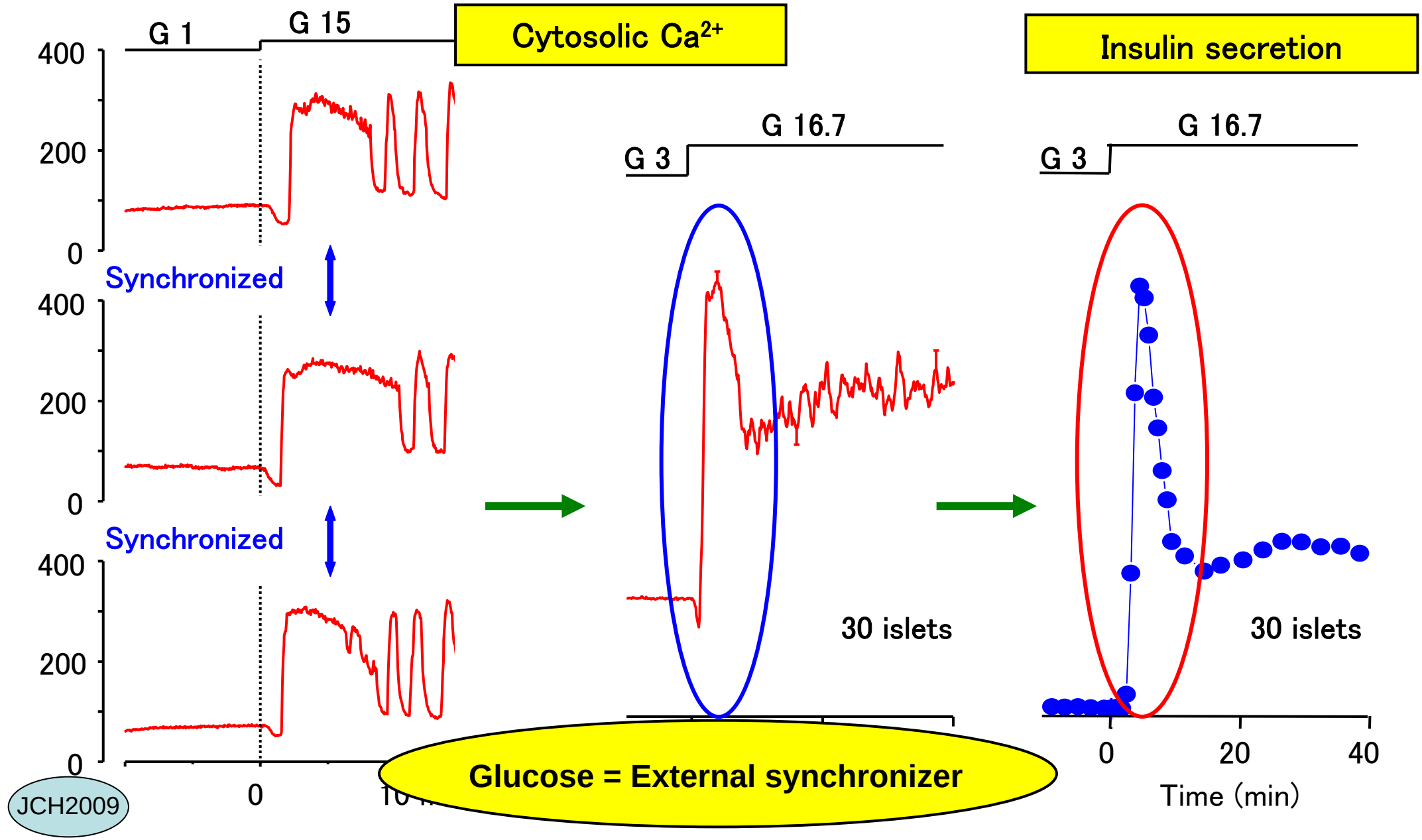
Rorsman and Renström, Diabetologia 2003

The time course of the triggering Ca^{2+} signal is more important than pools of granules to shape the kinetics of insulin secretion

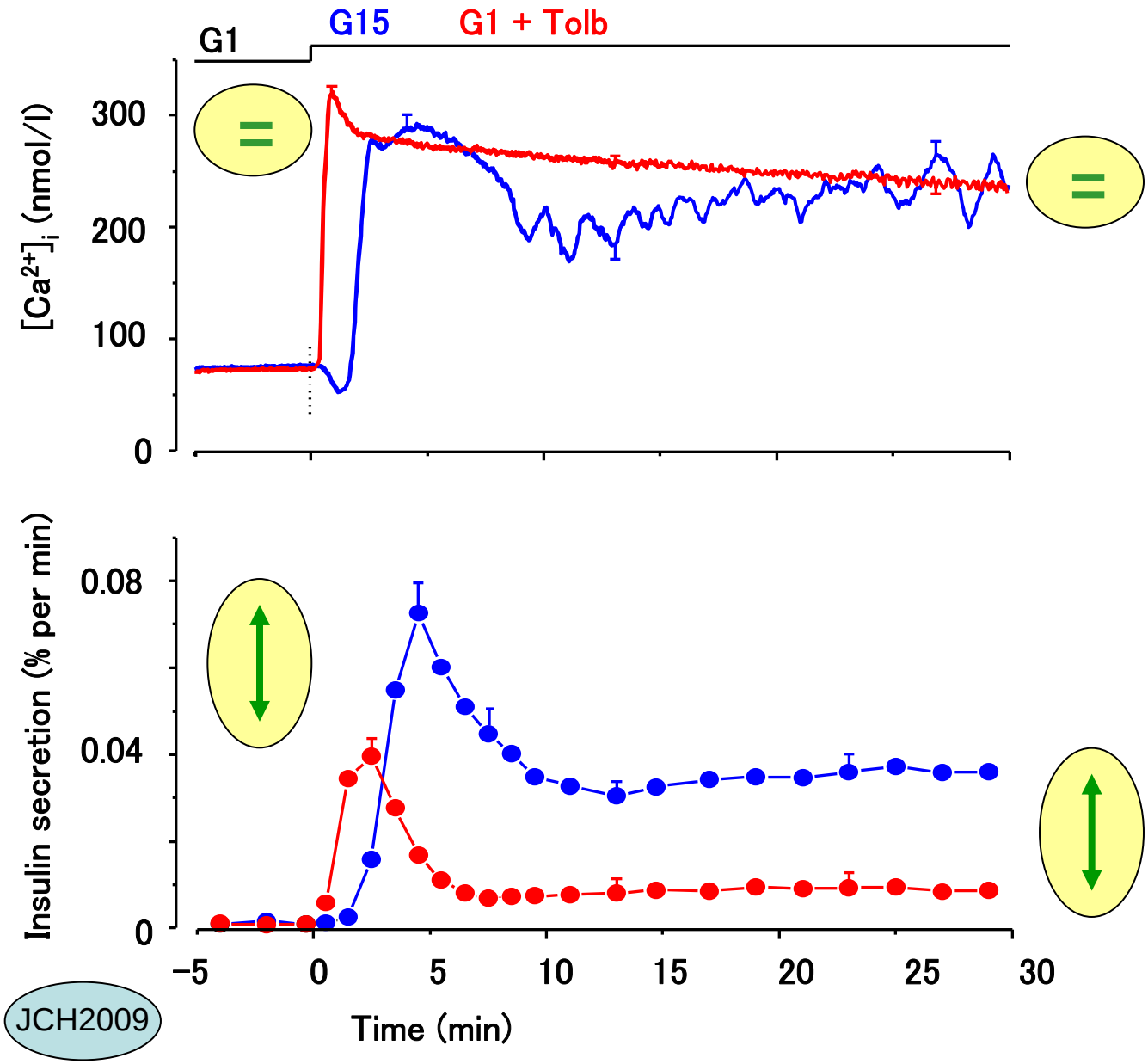
Biphasic $[Ca^{2+}]_c$ and insulin responses to glucose



Biphasic $[Ca^{2+}]_c$ and insulin responses to glucose



Triggering and amplifying pathways in biphasic GSIS



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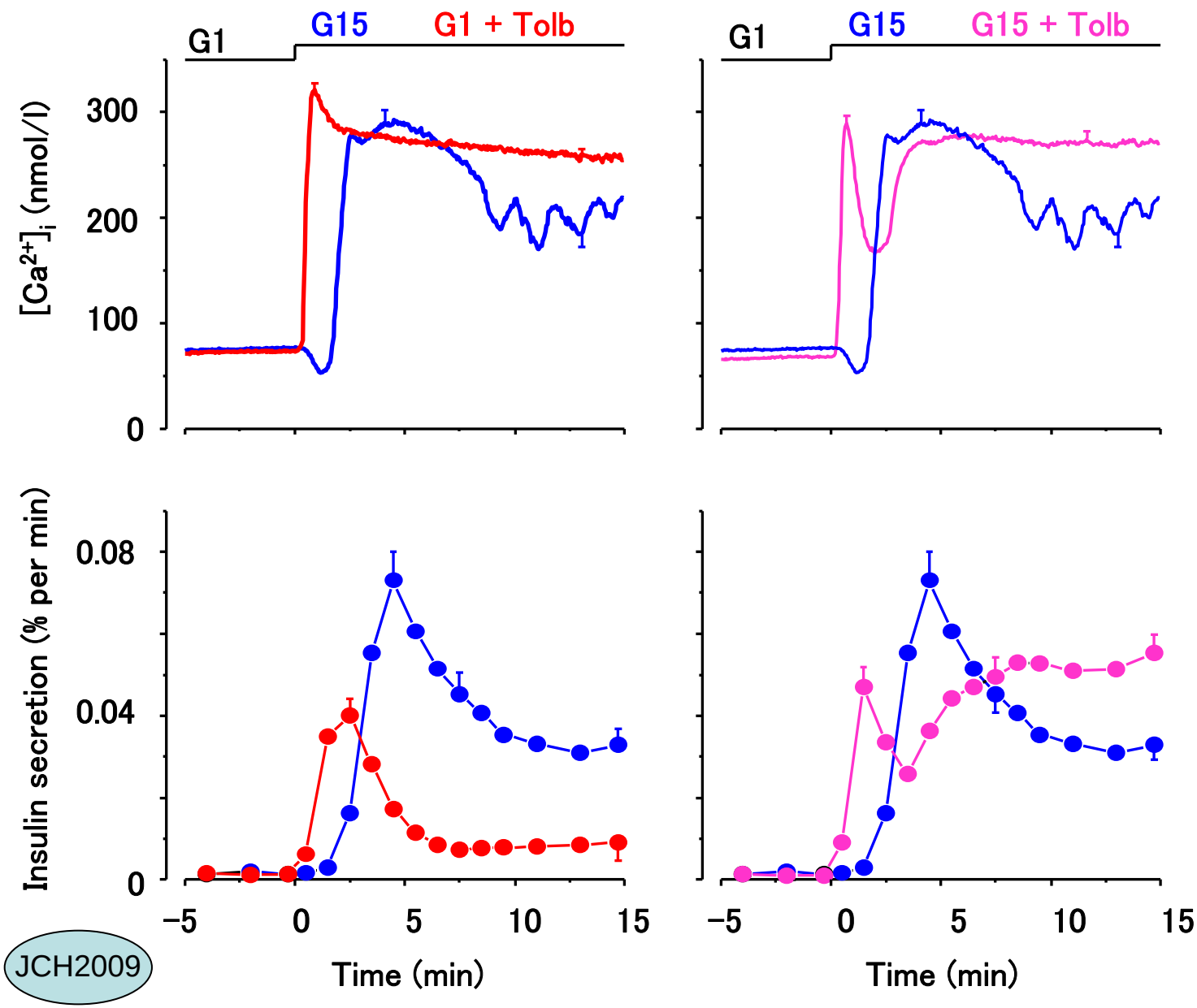
Amplification during first phase GSIS



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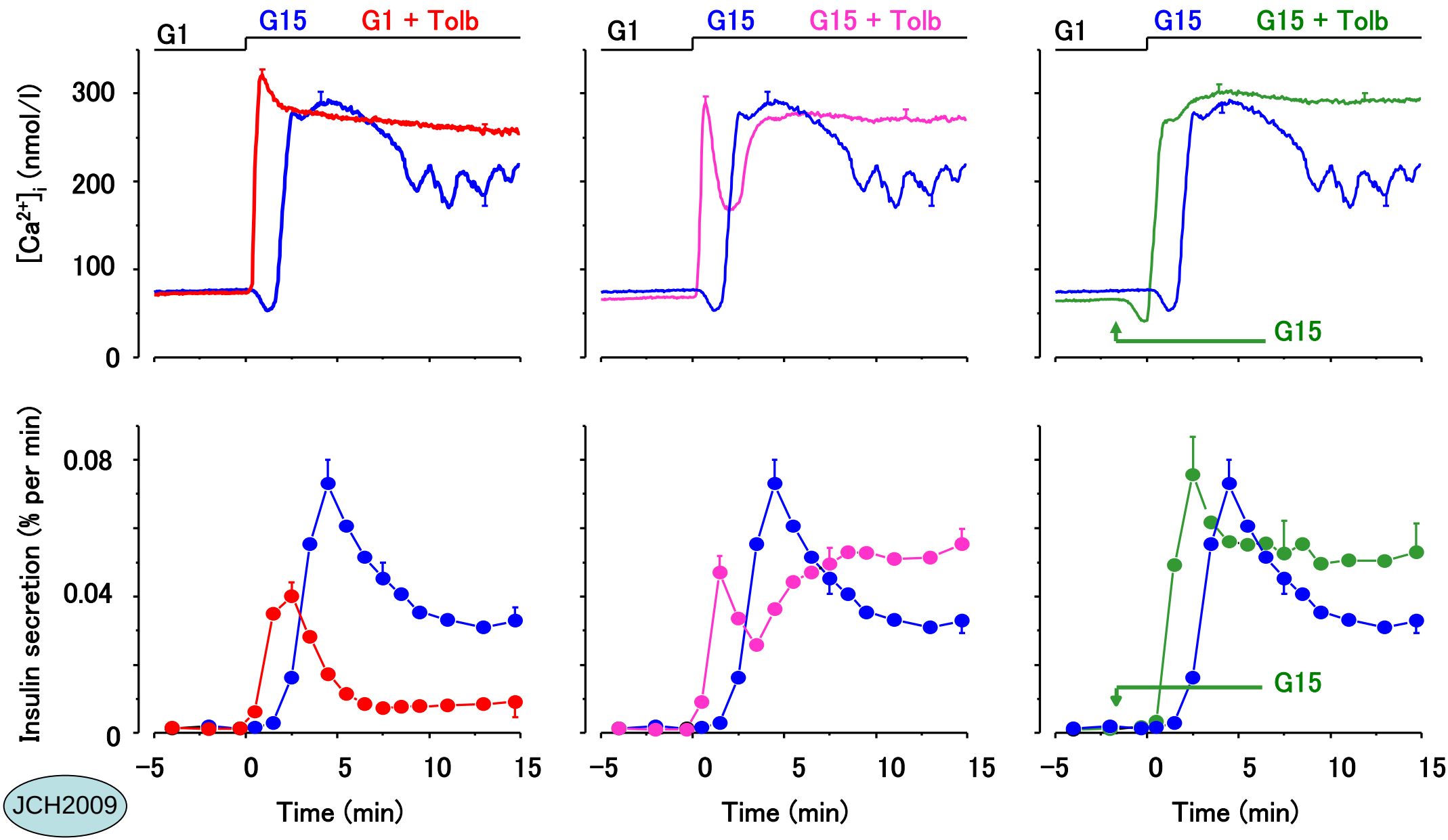
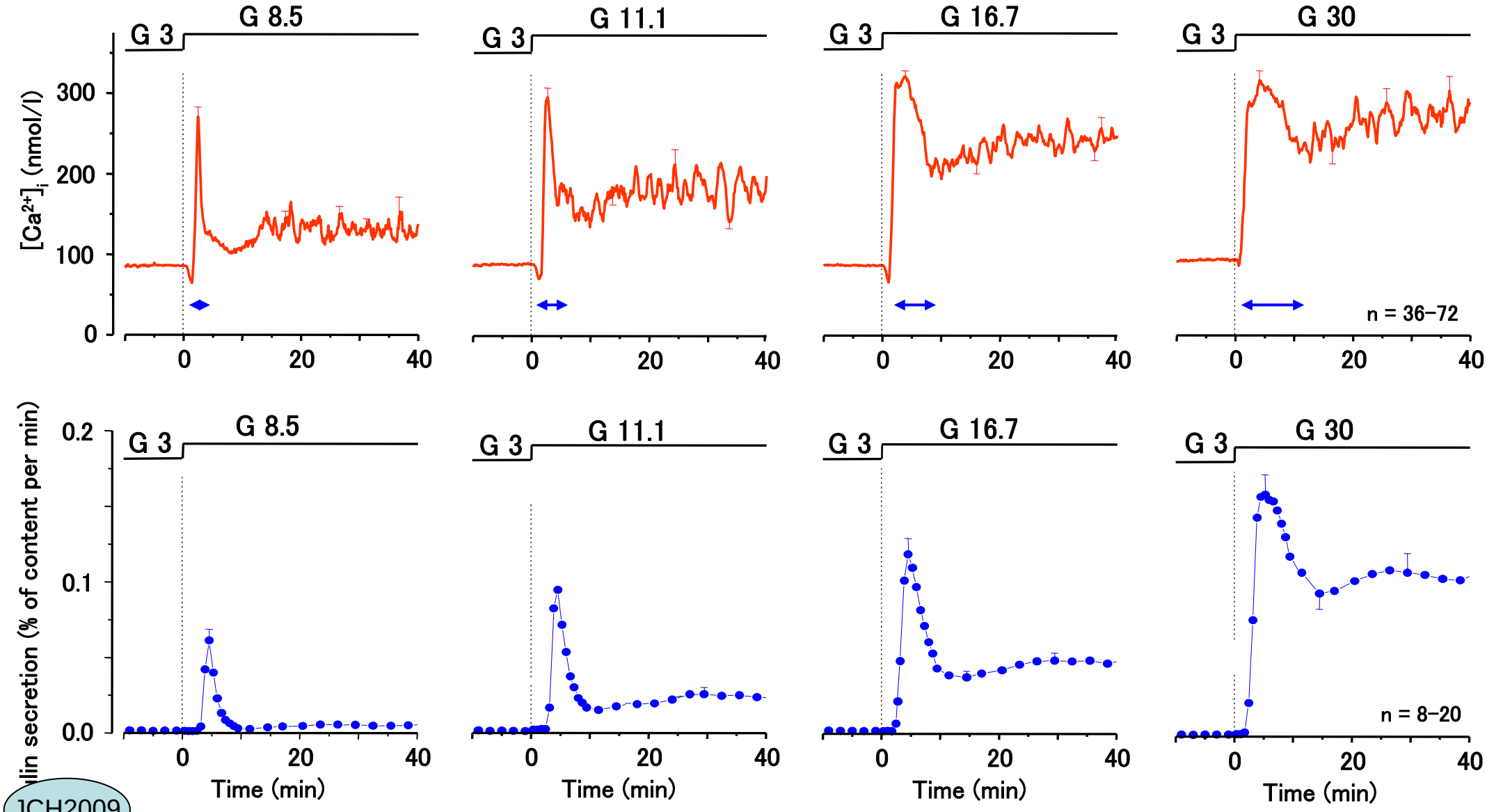
Amplification during first phase GSIS



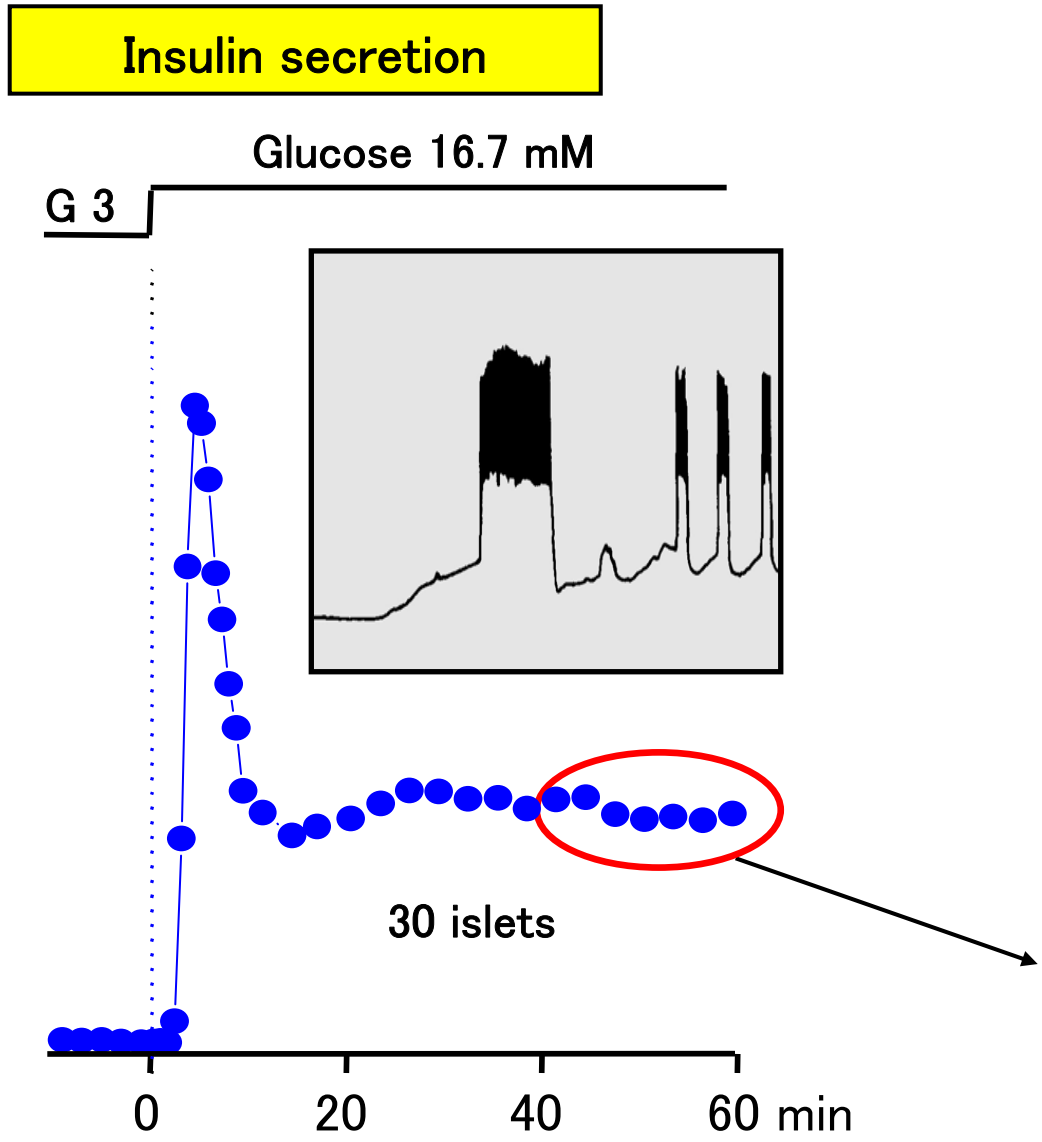
JCH2009

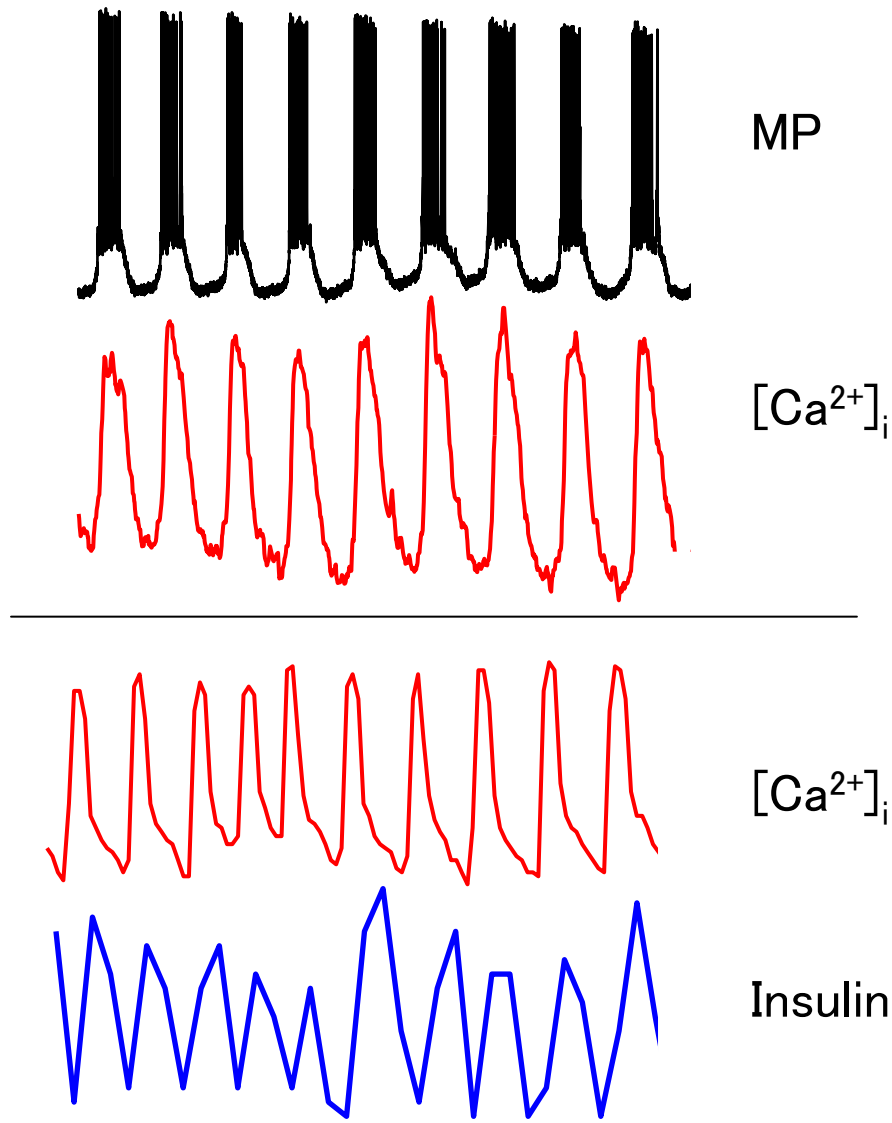
Biphasic $[Ca^{2+}]_c$ and insulin responses to glucose: a time control



JCH2009

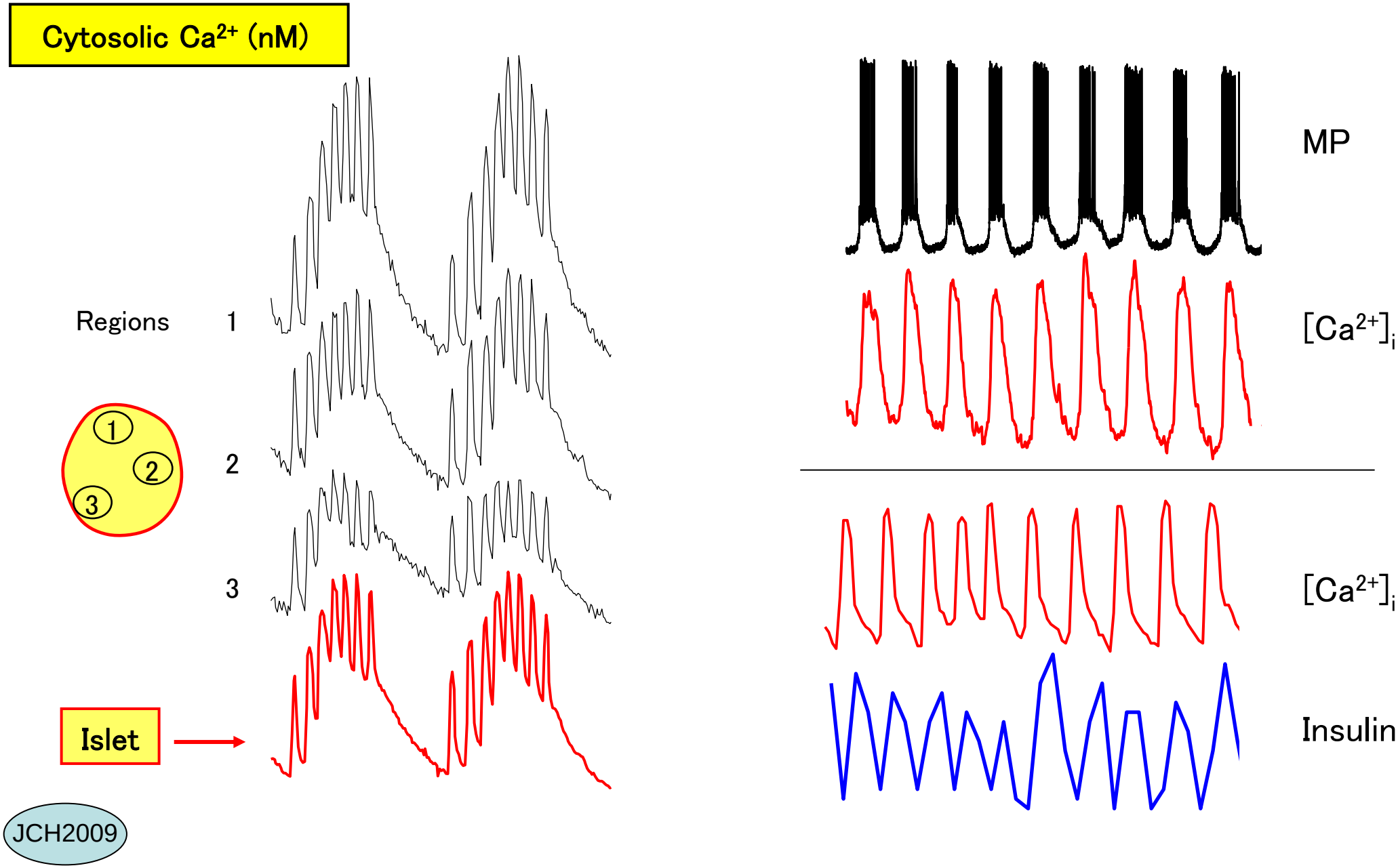
From synchronous electrical activity to pulsatile insulin secretion





JCH2009

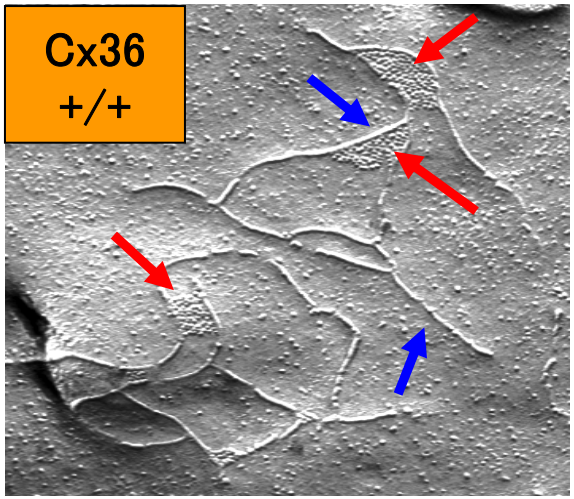
From synchronous electrical activity to pulsatile insulin secretion

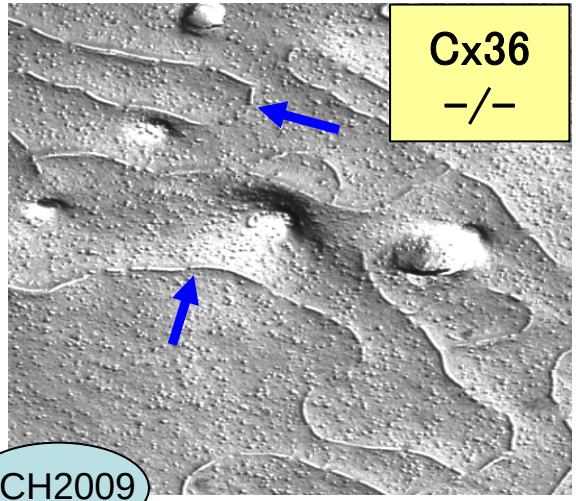


JCH2009

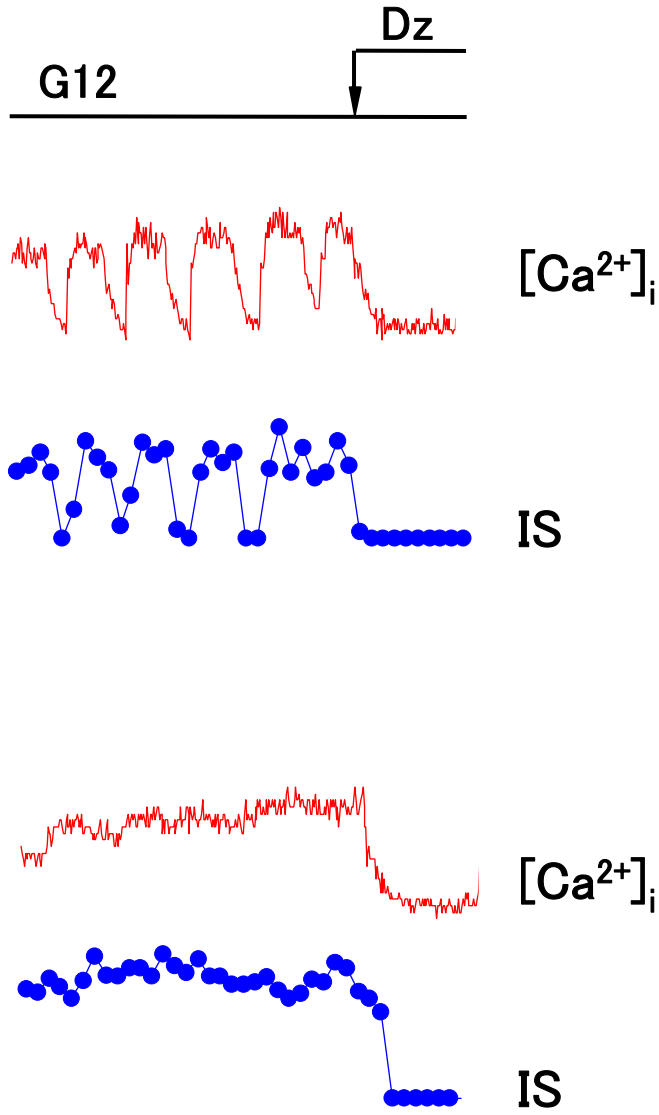
Gap junctions and oscillations of insulin secretion

Connexin-36





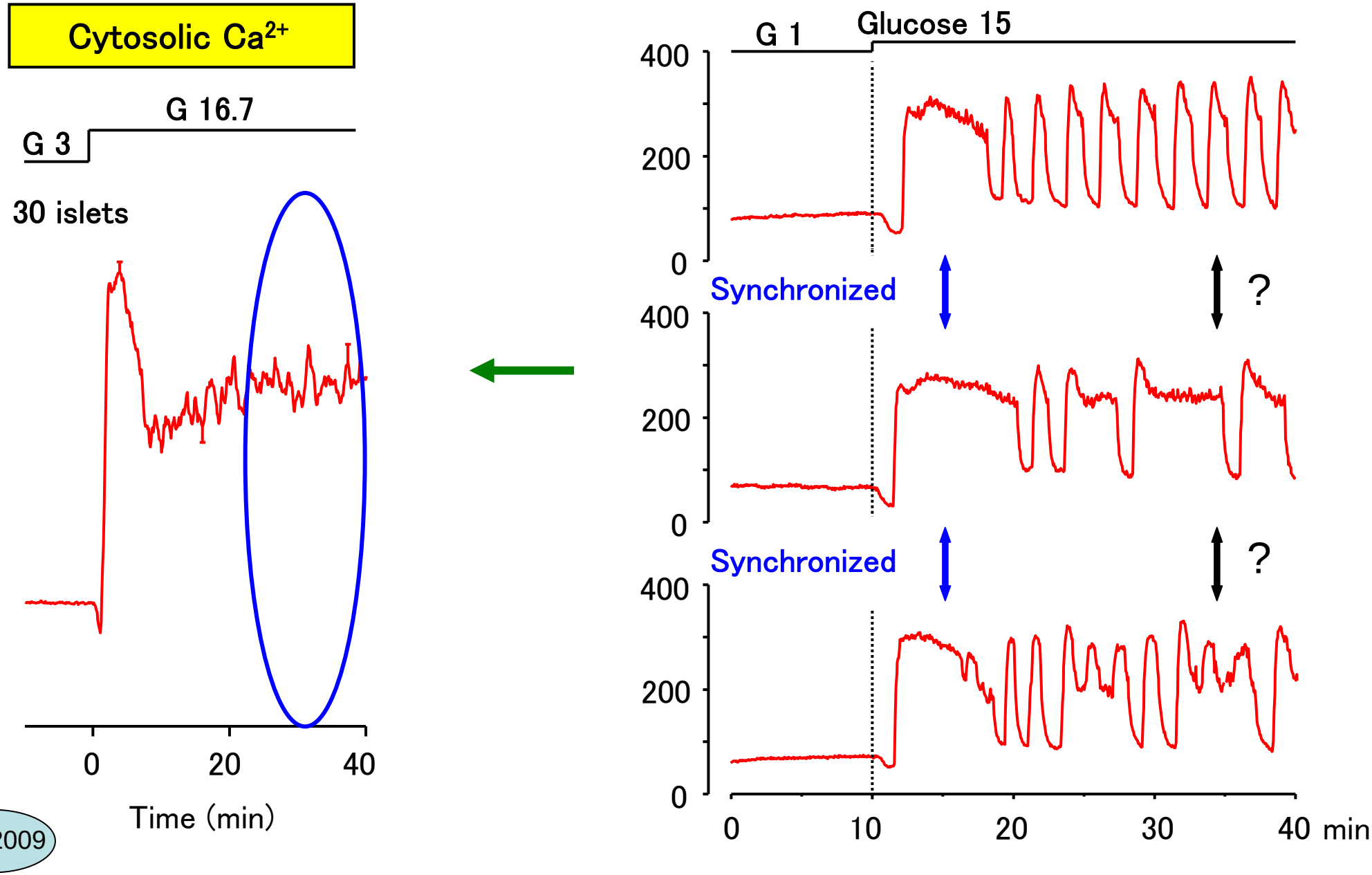
JCH2009



β-cell synchronization is achieved by electrical coupling through gap-junctions made of Connexin-36

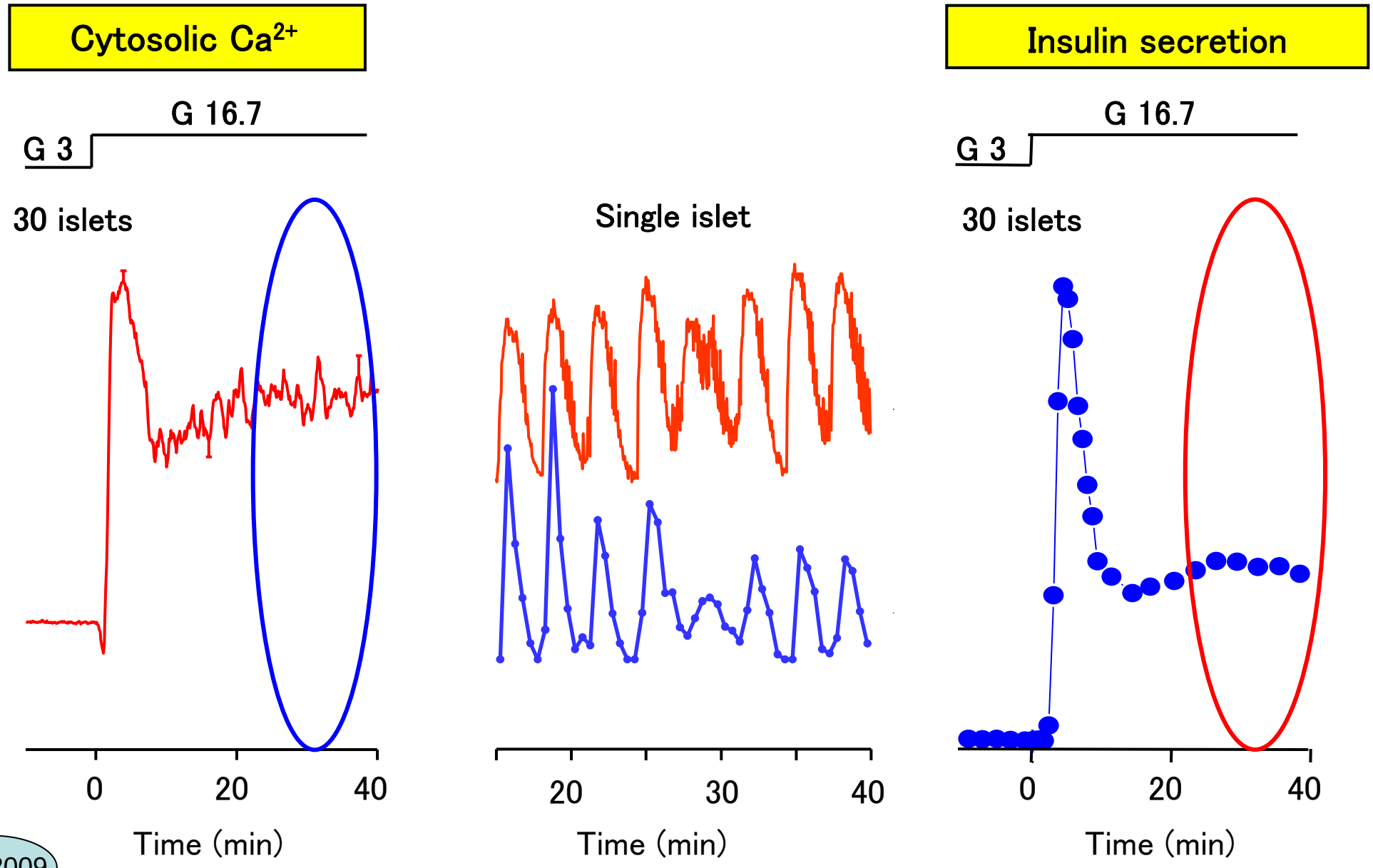
$[Ca^{2+}]_c$ oscillations are necessary for pulsatility of insulin secretion (IS)

Misinterpretation of glucose-induced $[Ca^{2+}]_c$ and insulin changes



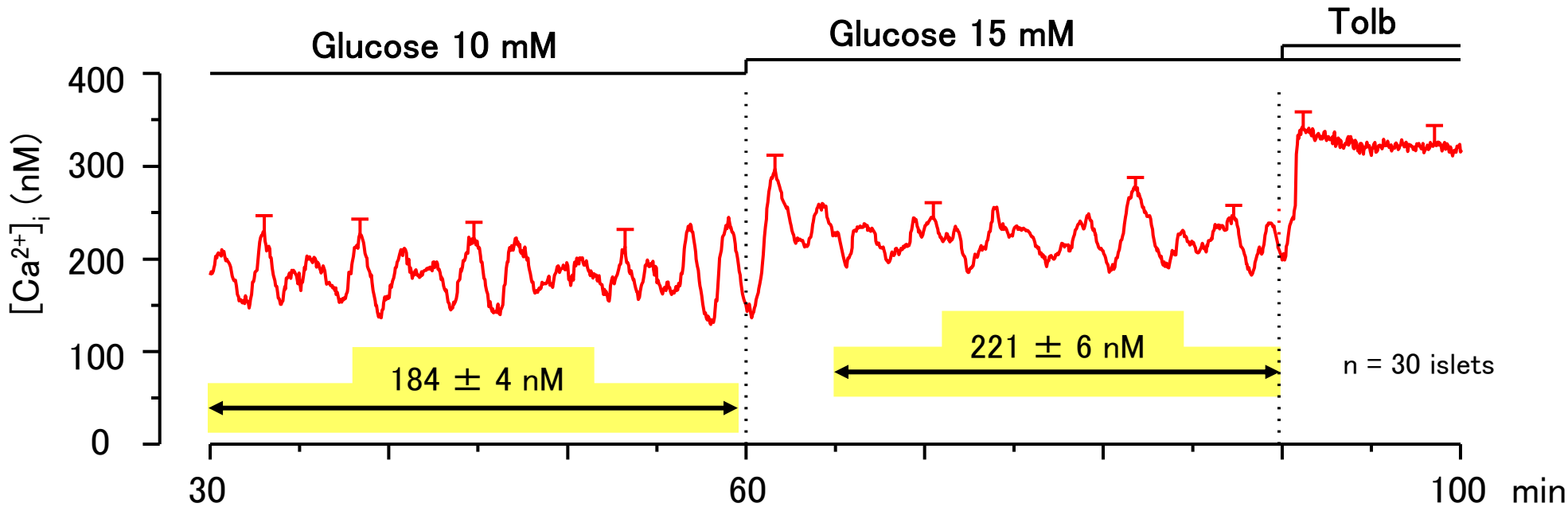
JCH2009

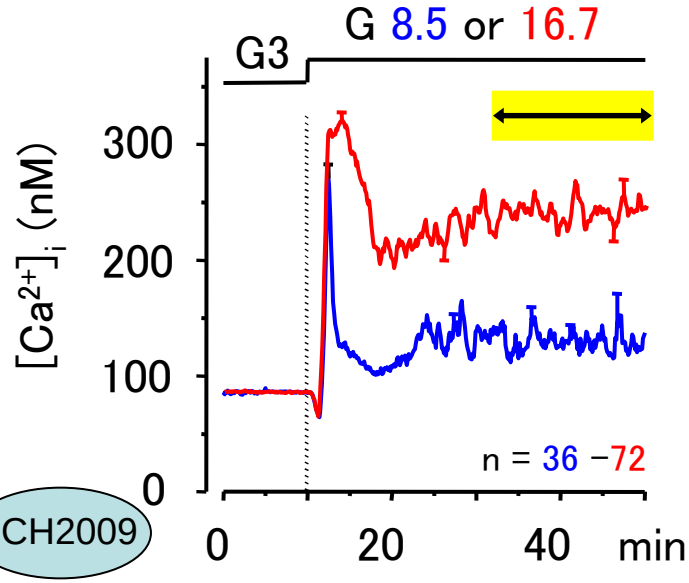
Misinterpretation of glucose-induced $[Ca^{2+}]_c$ and insulin changes

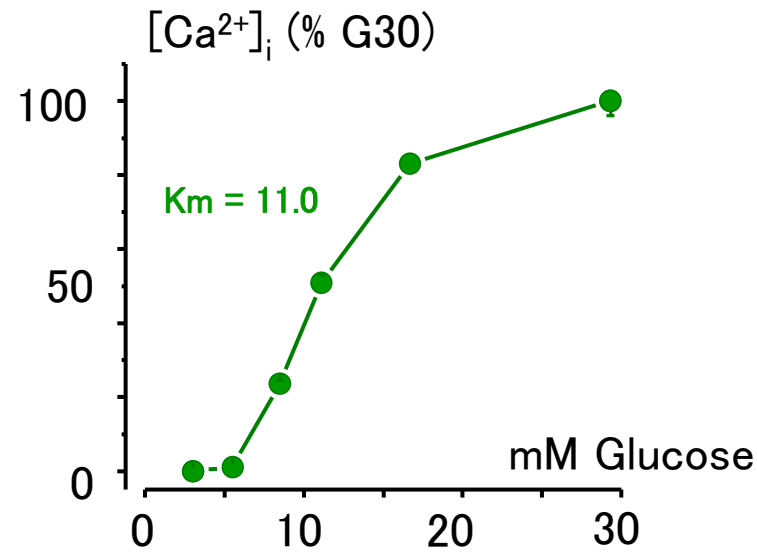


JCH2009

How does glucose control the $[Ca^{2+}]_c$ increase ?

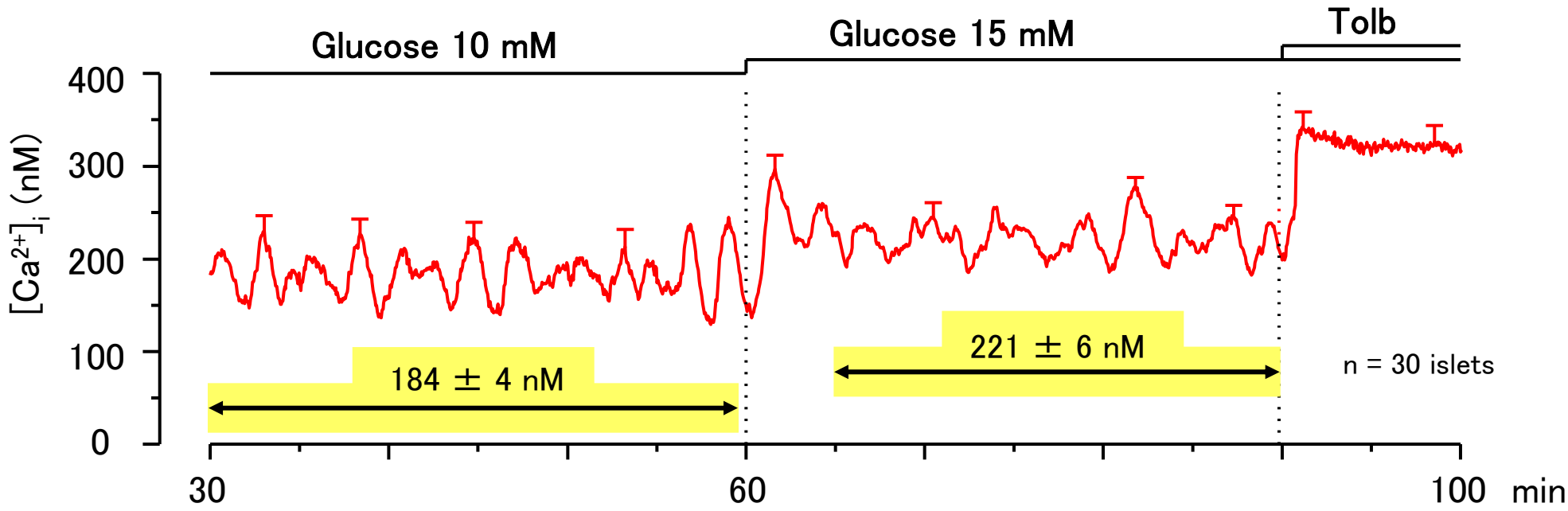


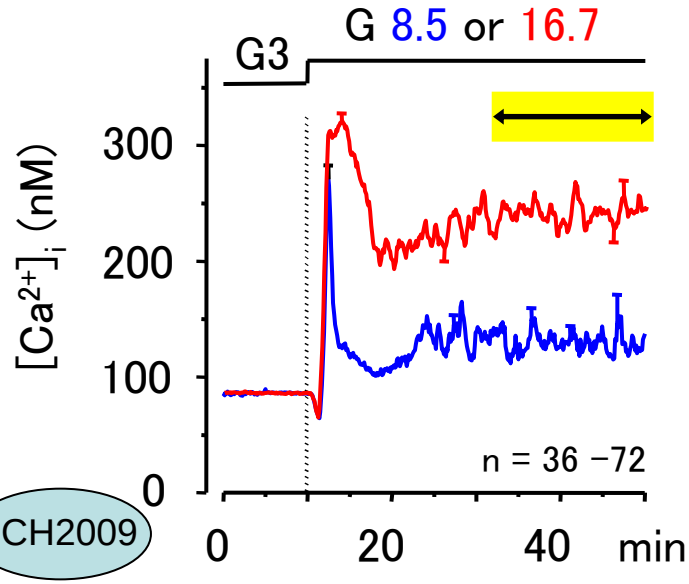




JCH2009

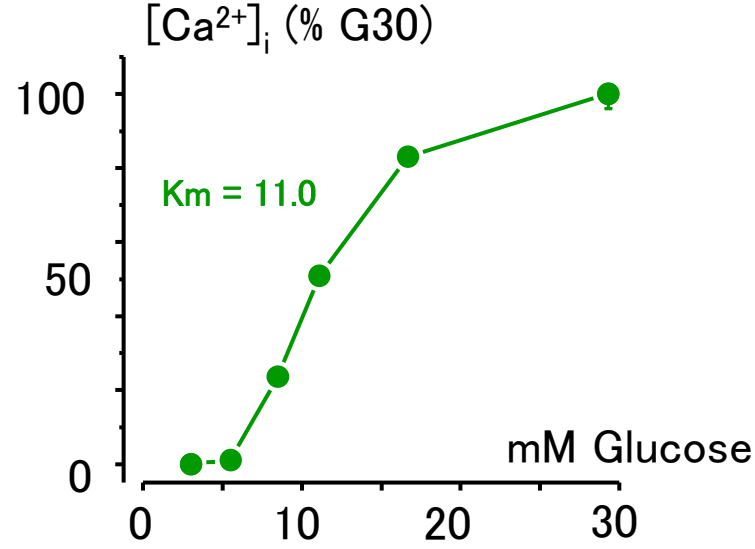
How does glucose control the $[Ca^{2+}]_c$ increase ?



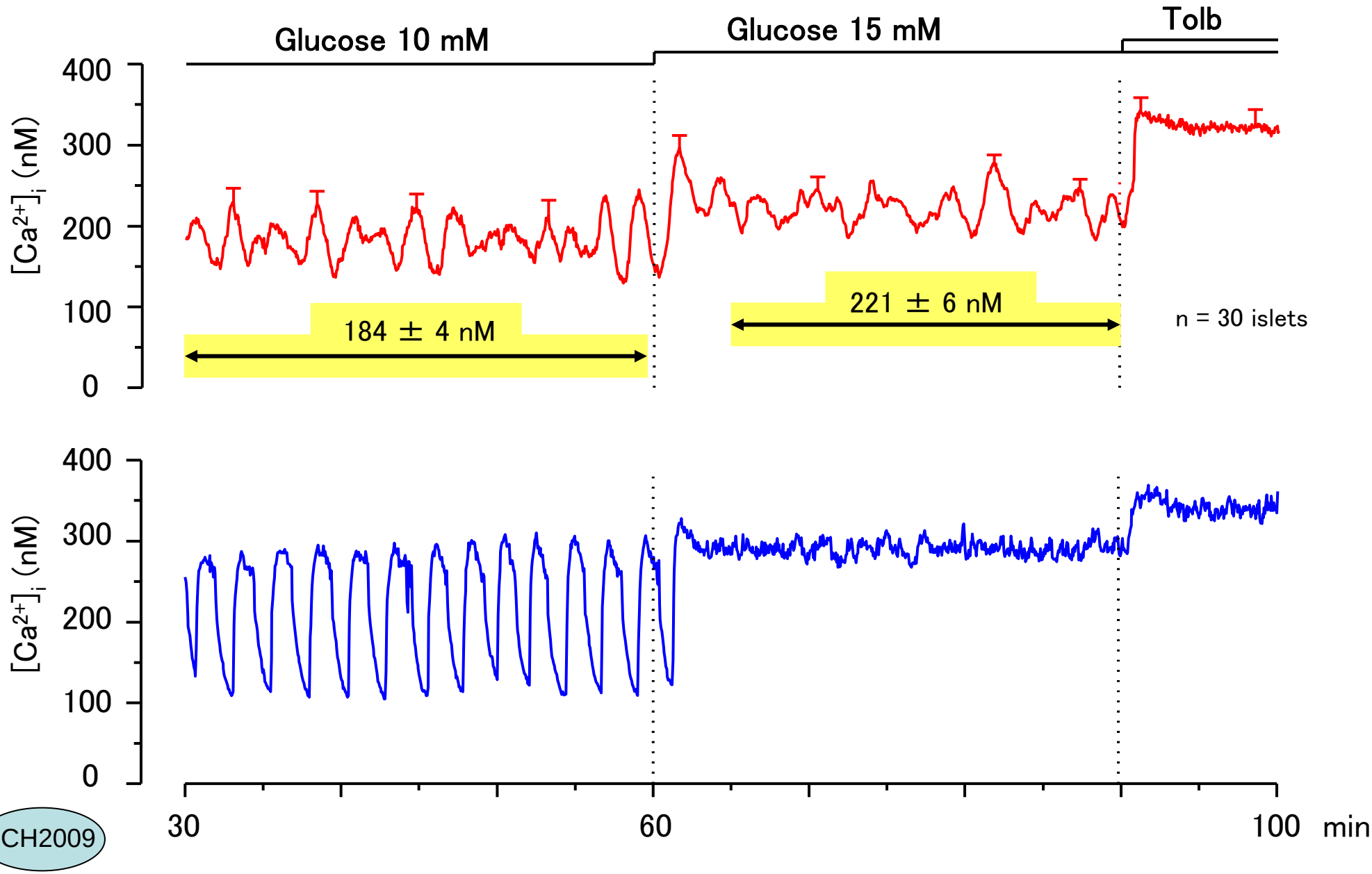


JCH2009

Amplitude modulation of triggering signal ?

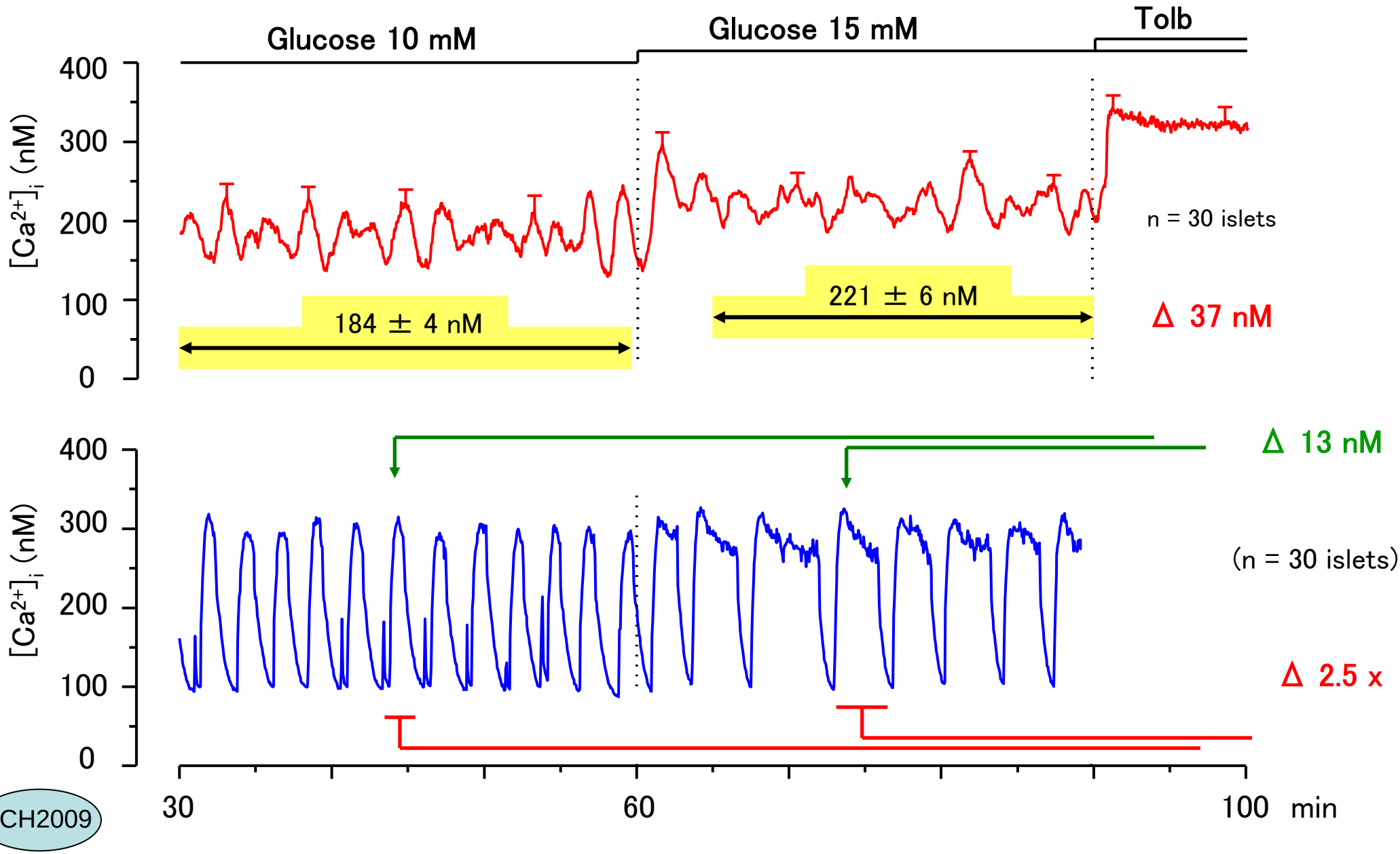


How does glucose control the $[Ca^{2+}]_c$ increase ?

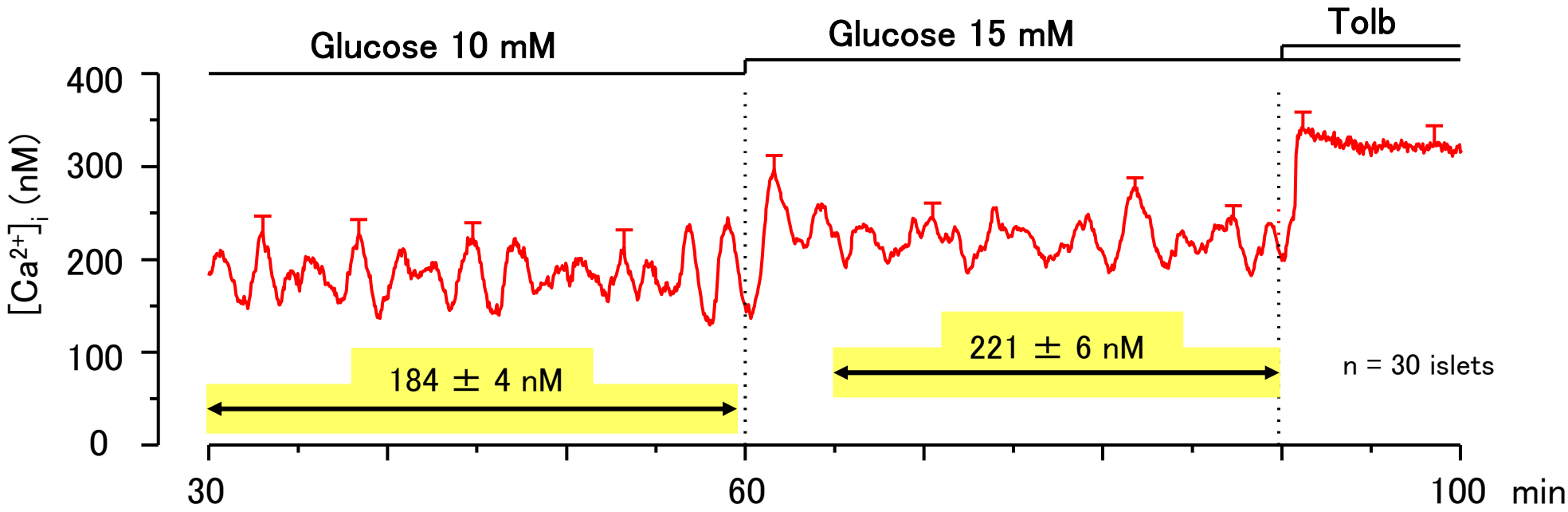


JCH2009

How does glucose control the $[Ca^{2+}]_c$ increase ?

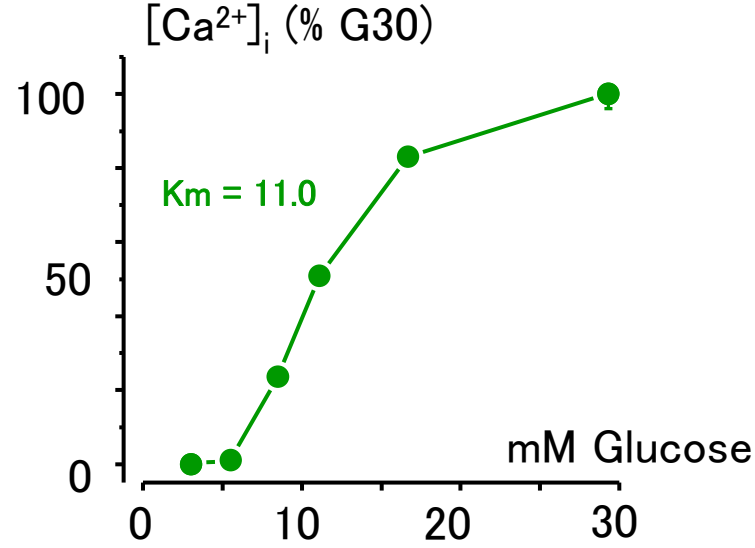


How does glucose control the $[Ca^{2+}]_c$ increase ?



Time control

Amplitude modulation ?



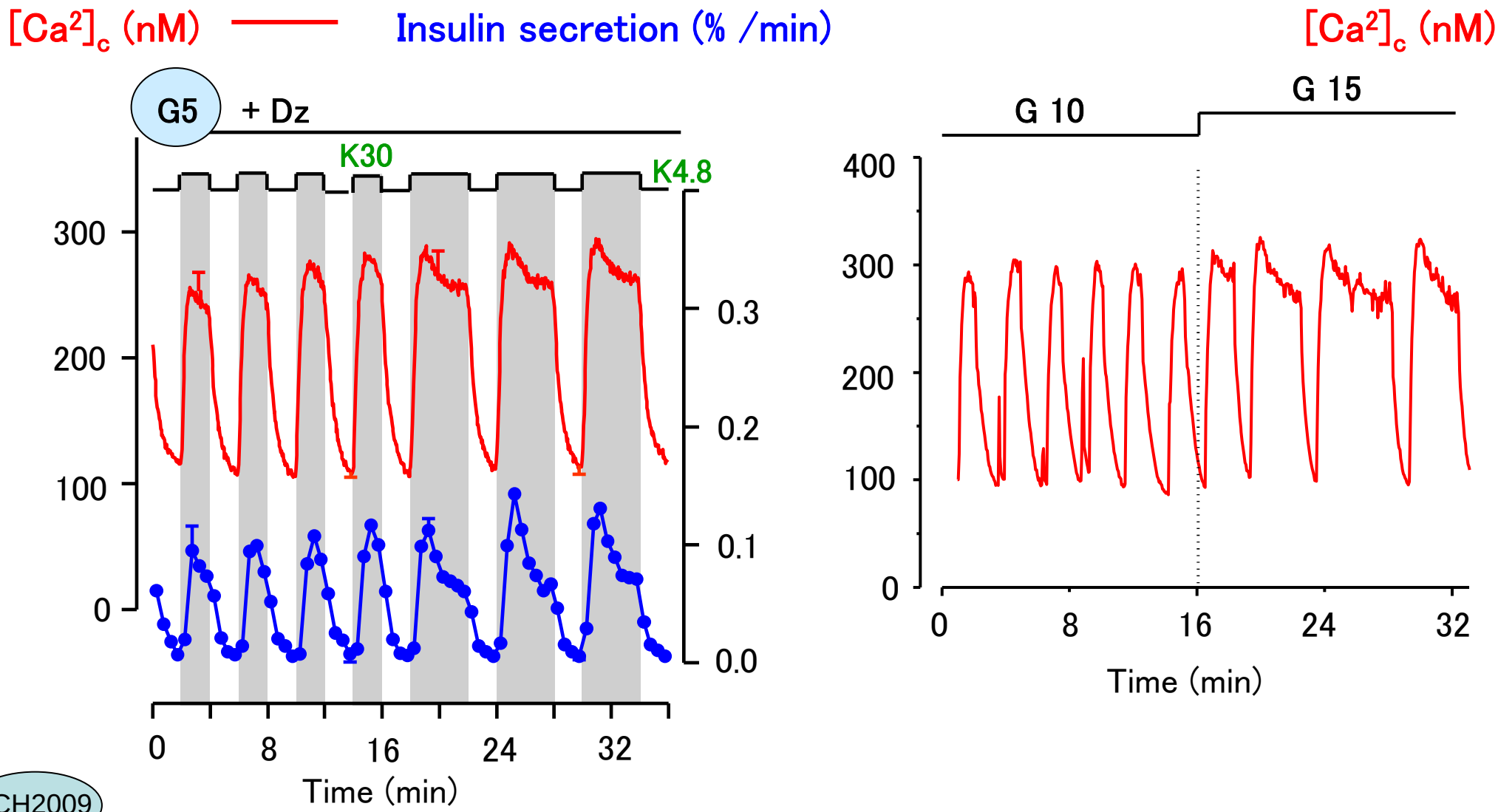
JCH2009

Subtle interaction of

time control and amplitude modulation

during second phase

Time and amplitude regulation of pulsatile insulin secretion



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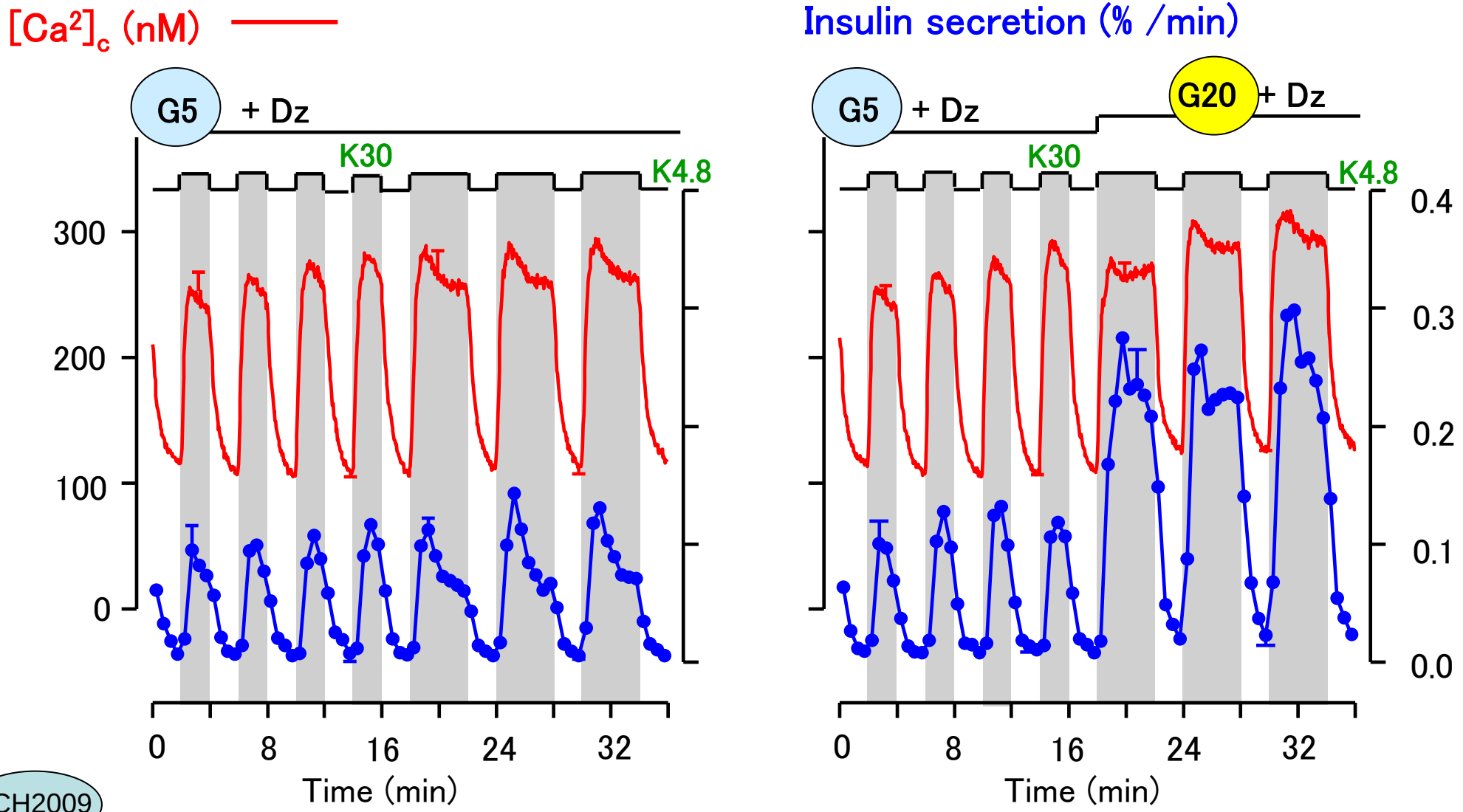
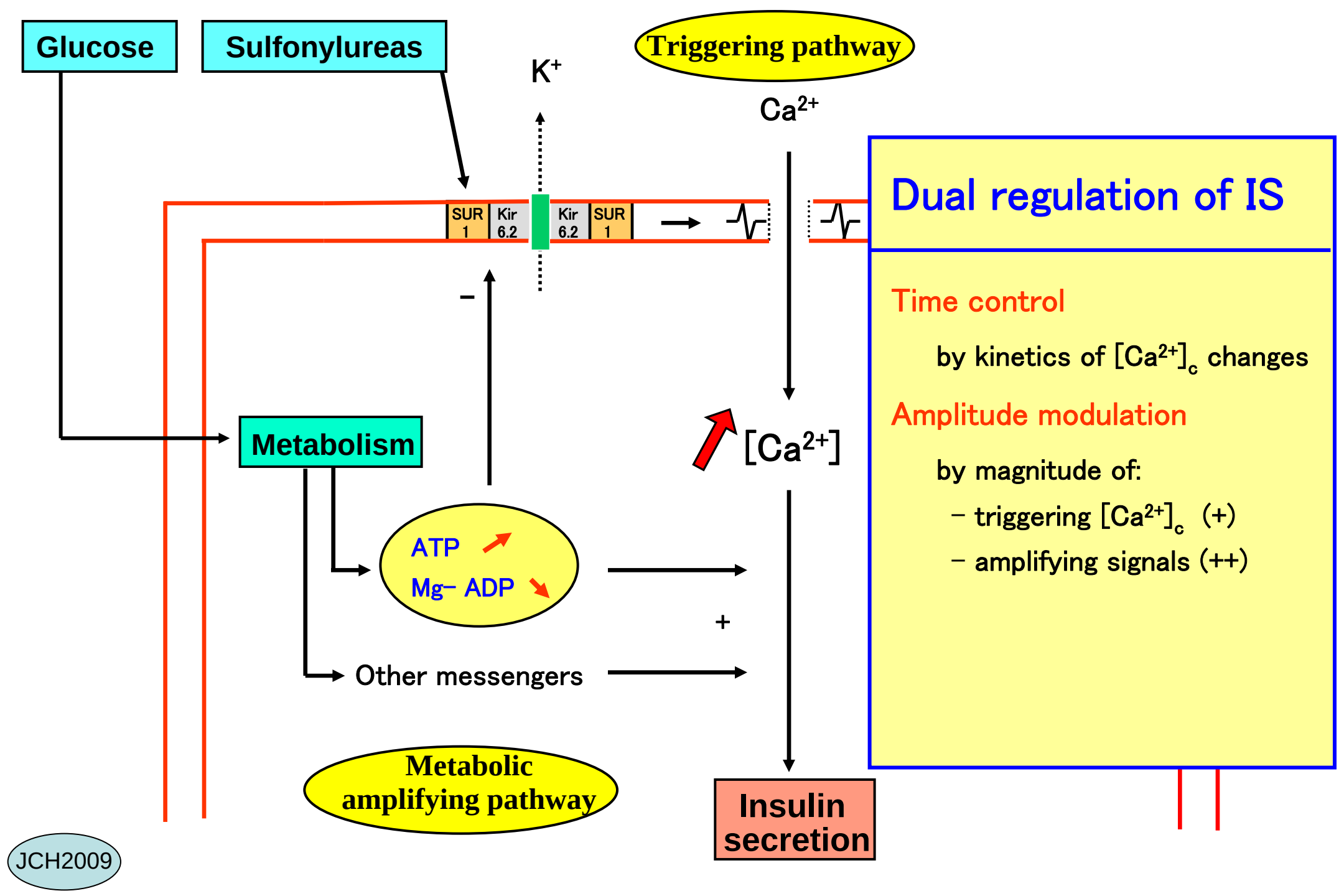
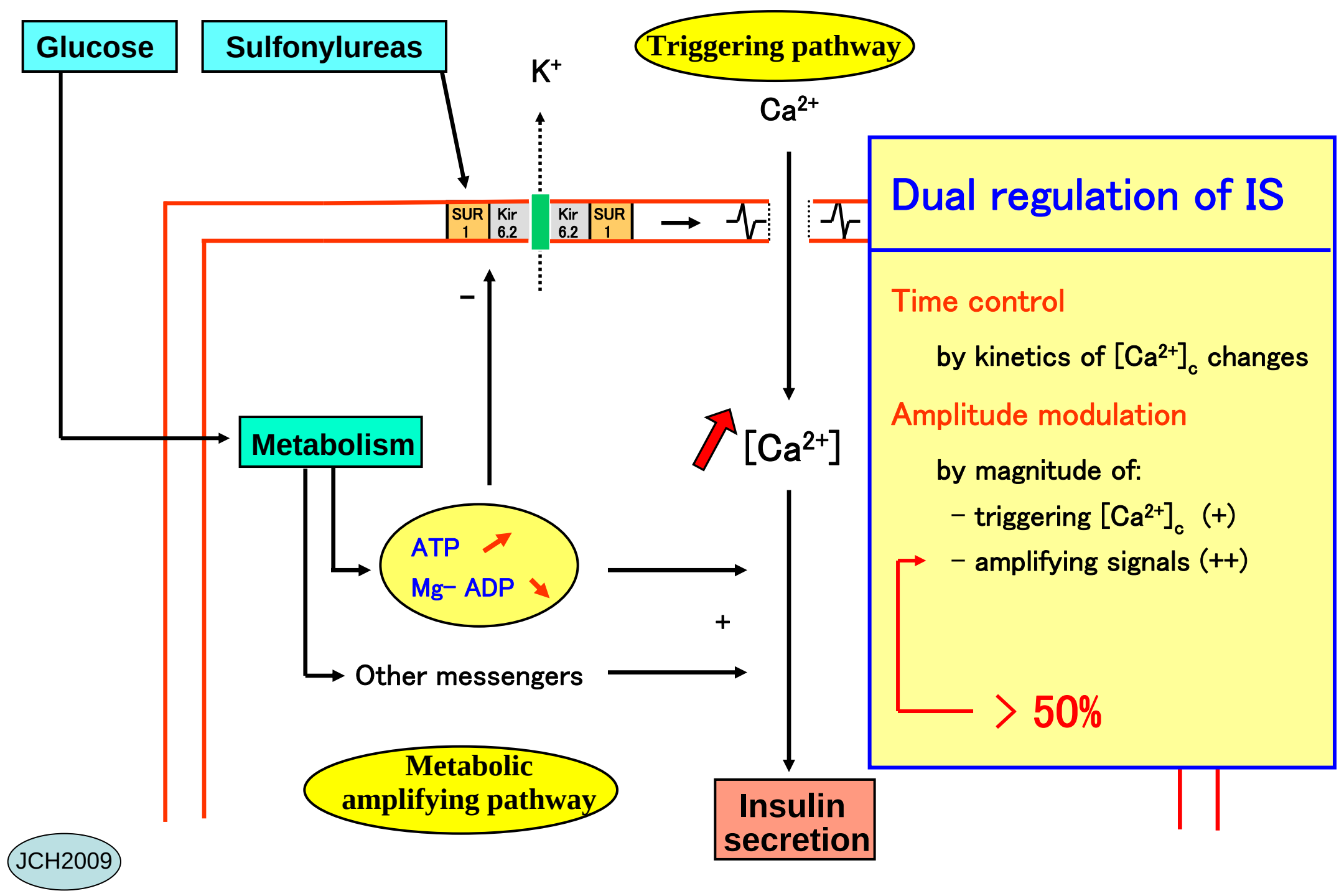
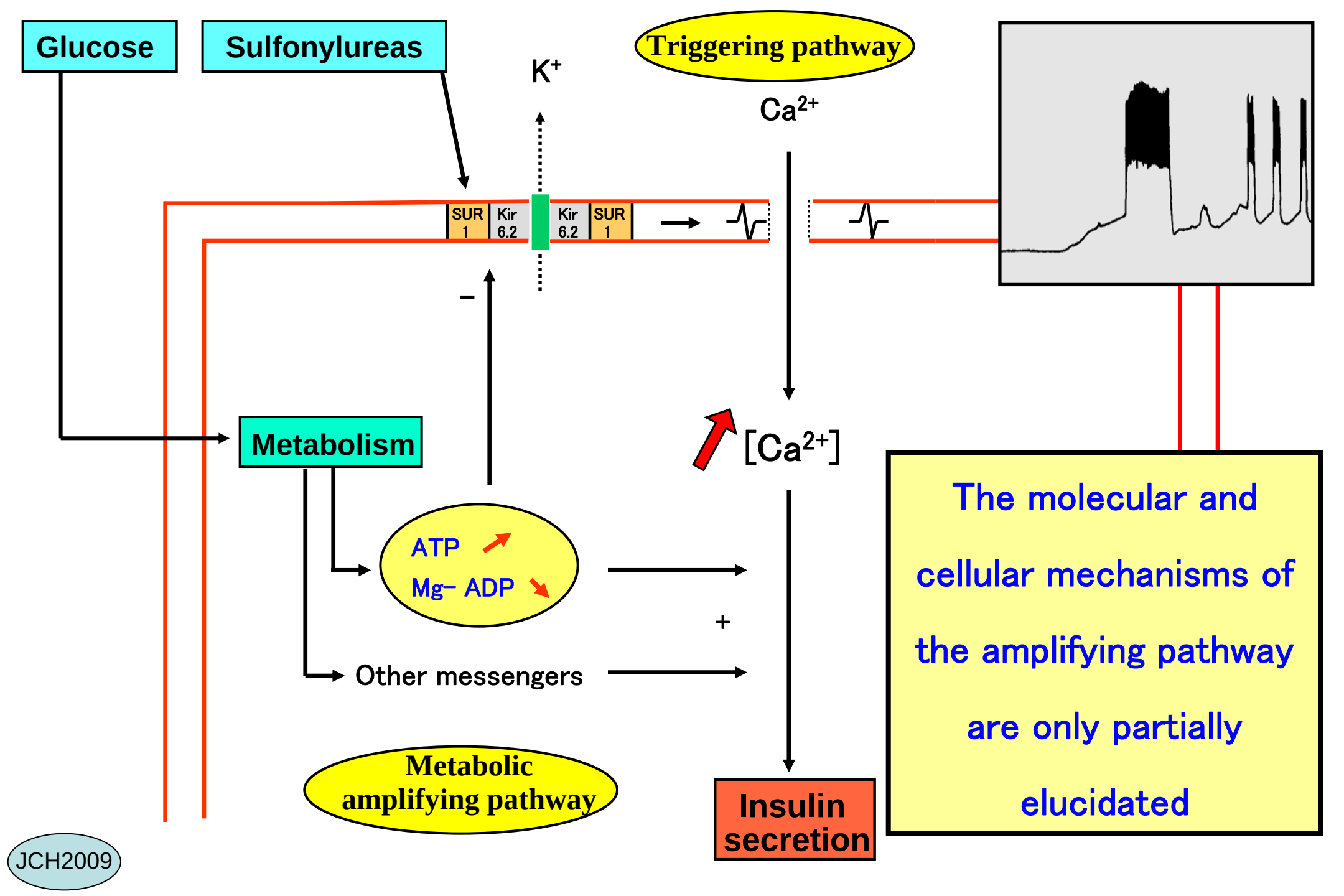
Time and amplitude regulation of pulsatile insulin secretion

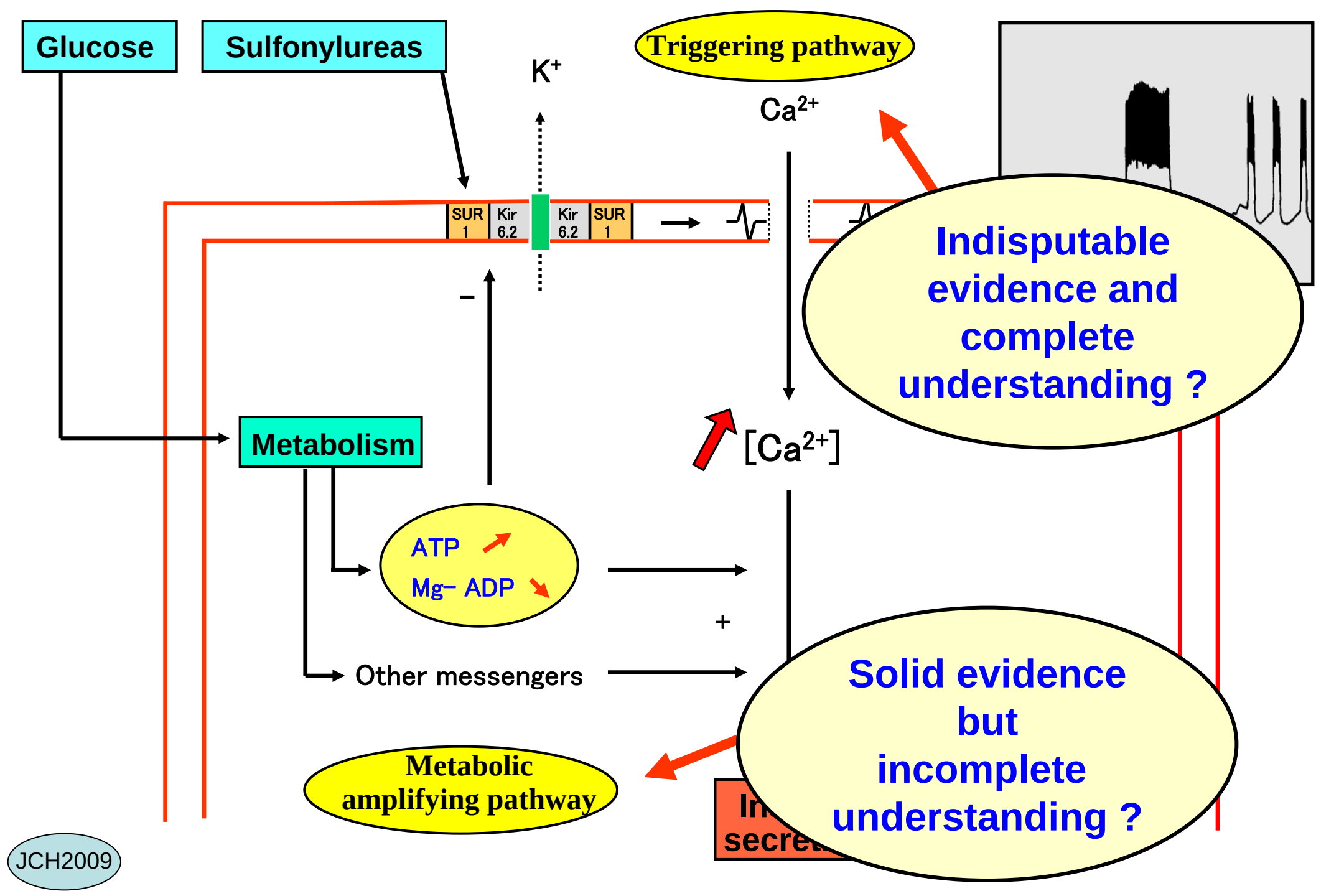


JCH2009

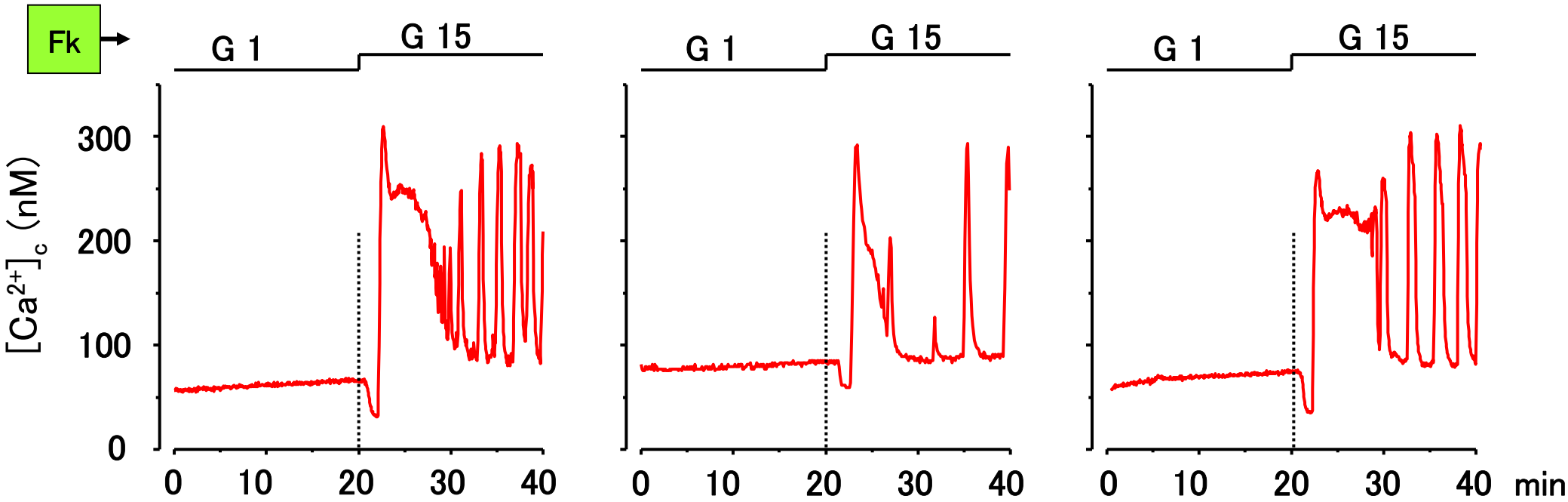

Glucose
Sulfonylureas
K+
Triggering pathway
Ca2+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
Dual regulation of IS
Time control
by kinetics of [Ca2+]c changes
Amplitude modulation
by magnitude of:
– triggering [Ca2+]c (+)
– amplifying signals (++)
–
Metabolism
[Ca2+]
ATP
Mg– ADP
+
Other messengers
Metabolic amplifying pathway
Insulin secretion
JCH2009


Glucose
Sulfonylureas
K+
Triggering pathway
Ca2+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
Dual regulation of IS
Time control
by kinetics of [Ca2+]c changes
Amplitude modulation
by magnitude of:
– triggering [Ca2+]c (+)
– amplifying signals (++)
> 50%
–
Metabolism
[Ca2+]
ATP
Mg– ADP
+
Other messengers
Metabolic amplifying pathway
Insulin secretion
JCH2009


Glucose
Sulfonylureas
K+
Triggering pathway
Ca2+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
−
Metabolism
[Ca2+]
ATP
Mg− ADP
+
Other messengers
Metabolic amplifying pathway
Insulin secretion
The molecular and cellular mechanisms of the amplifying pathway are only partially elucidated
JCH2009

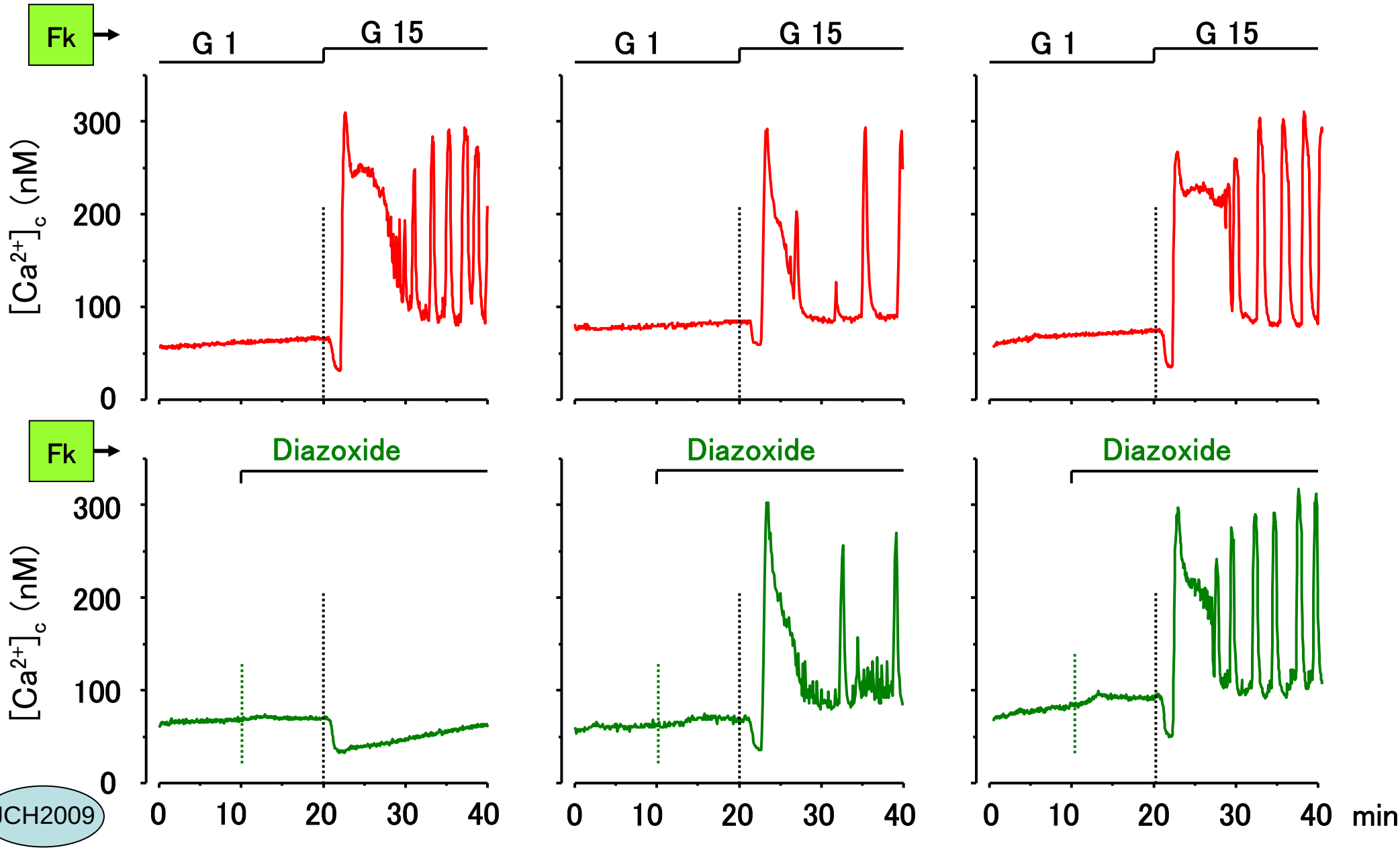

Glucose
Sulfonylureas
K+
Triggering pathway
Ca2+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
Indisputable evidence and complete understanding ?
–
Metabolism
[Ca2+]
ATP
Mg– ADP
+
Other messengers
Solid evidence but incomplete understanding ?
Metabolic amplifying pathway
JCH2009

Glucose-induced biphasic responses in 2w-old islets cultured in 5 mM Glucose

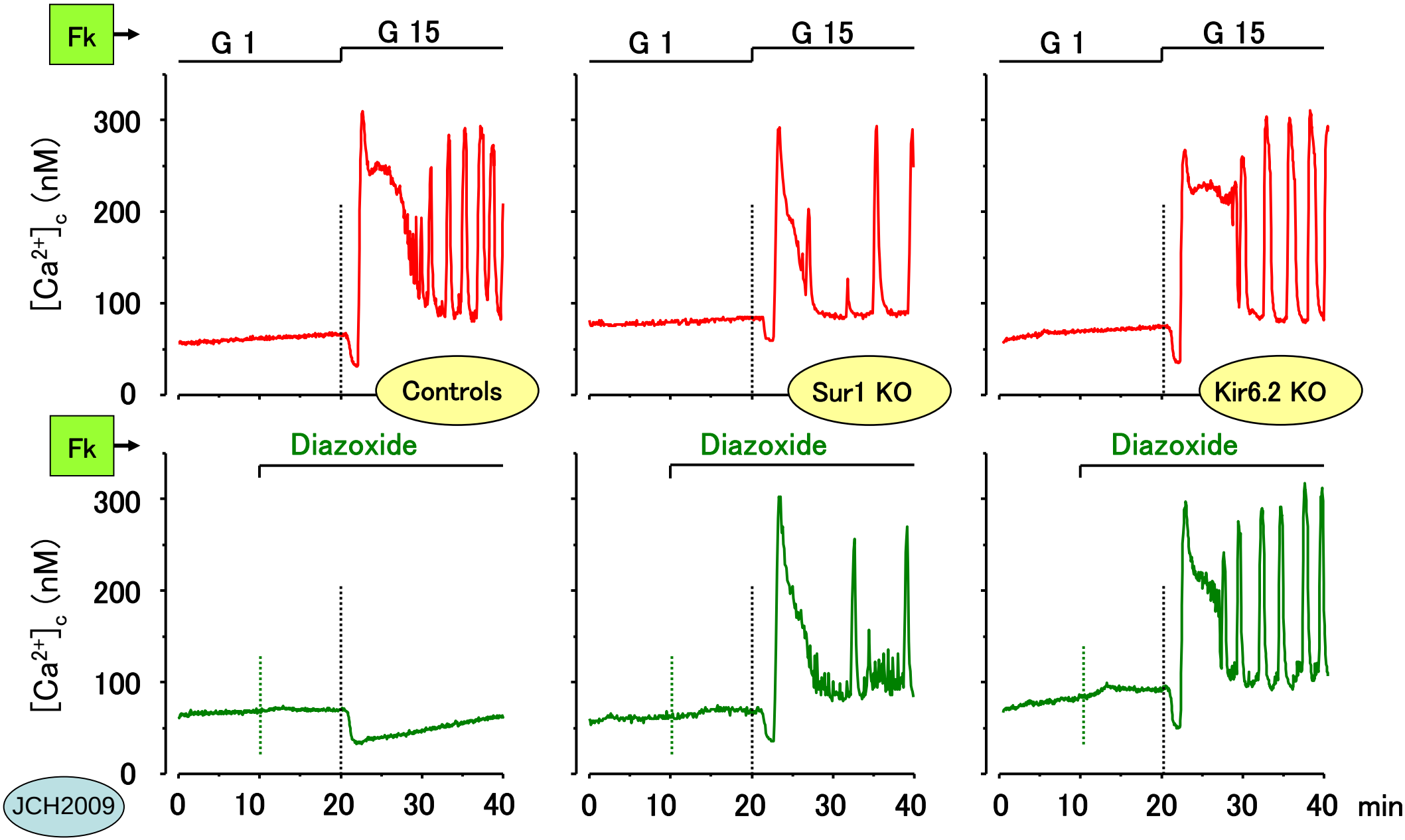


JCH2009

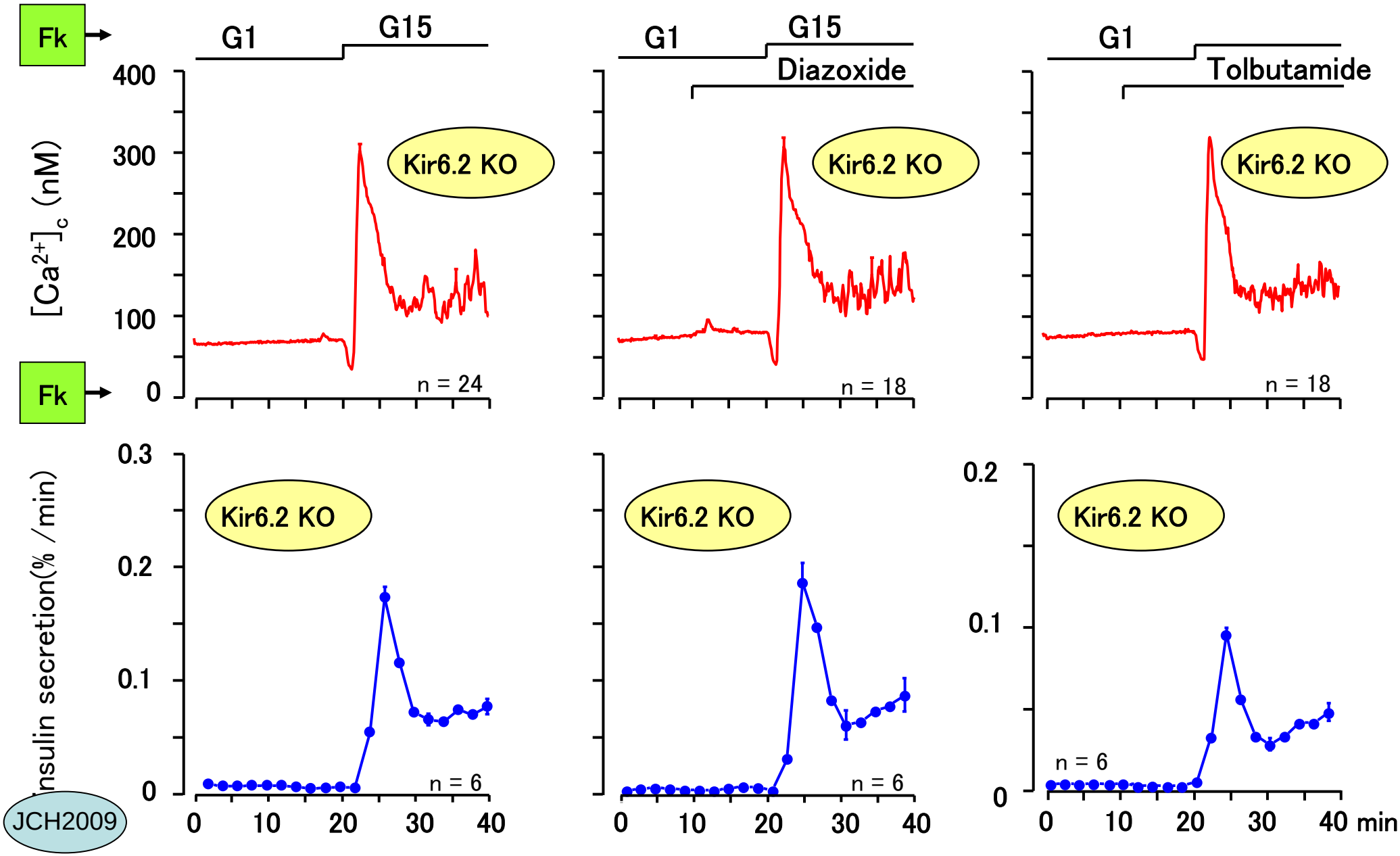
Glucose-induced biphasic responses in 2w-old islets cultured in 5 mM Glucose



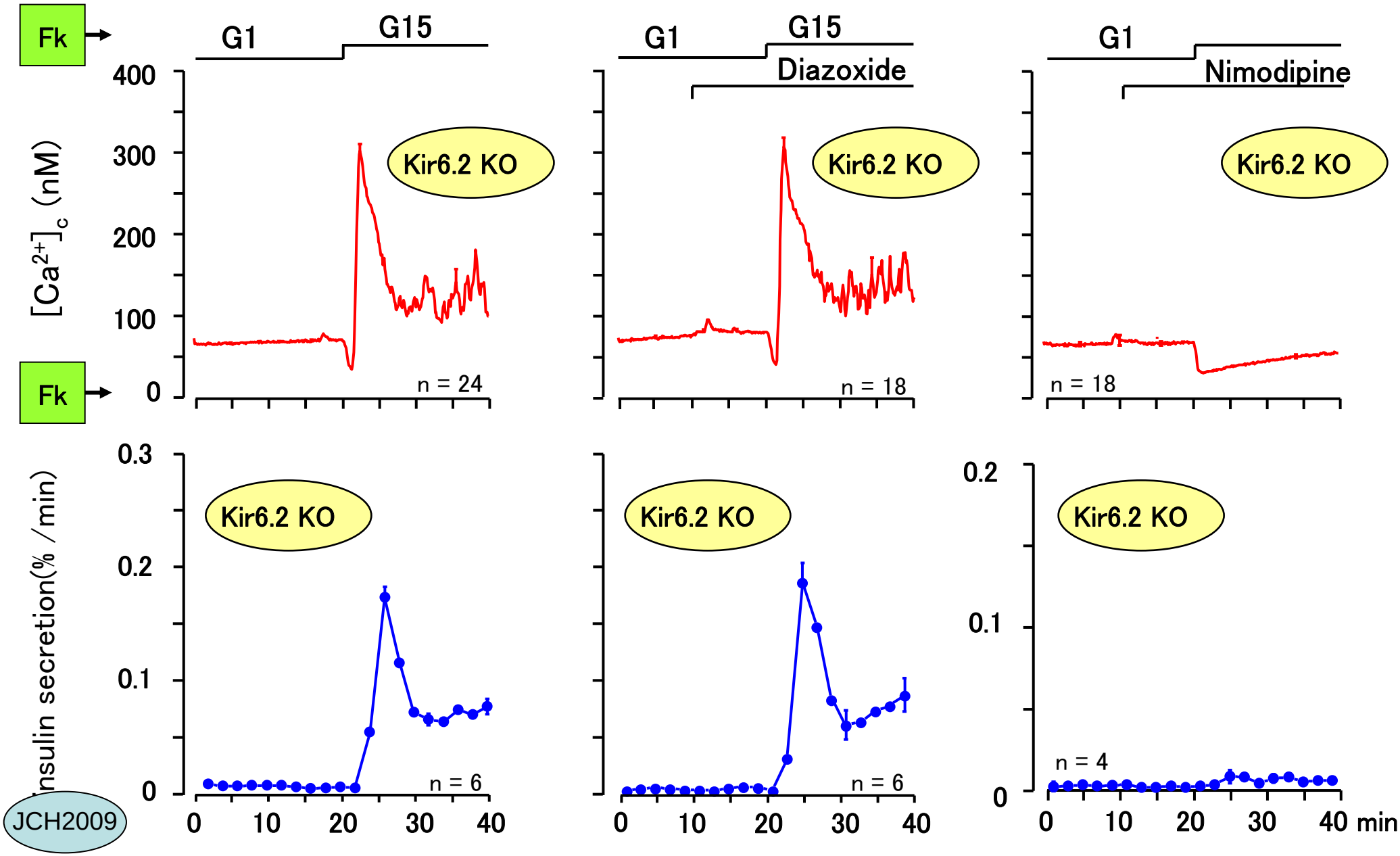
Glucose-induced biphasic responses in 2w-old islets cultured in 5 mM Glucose

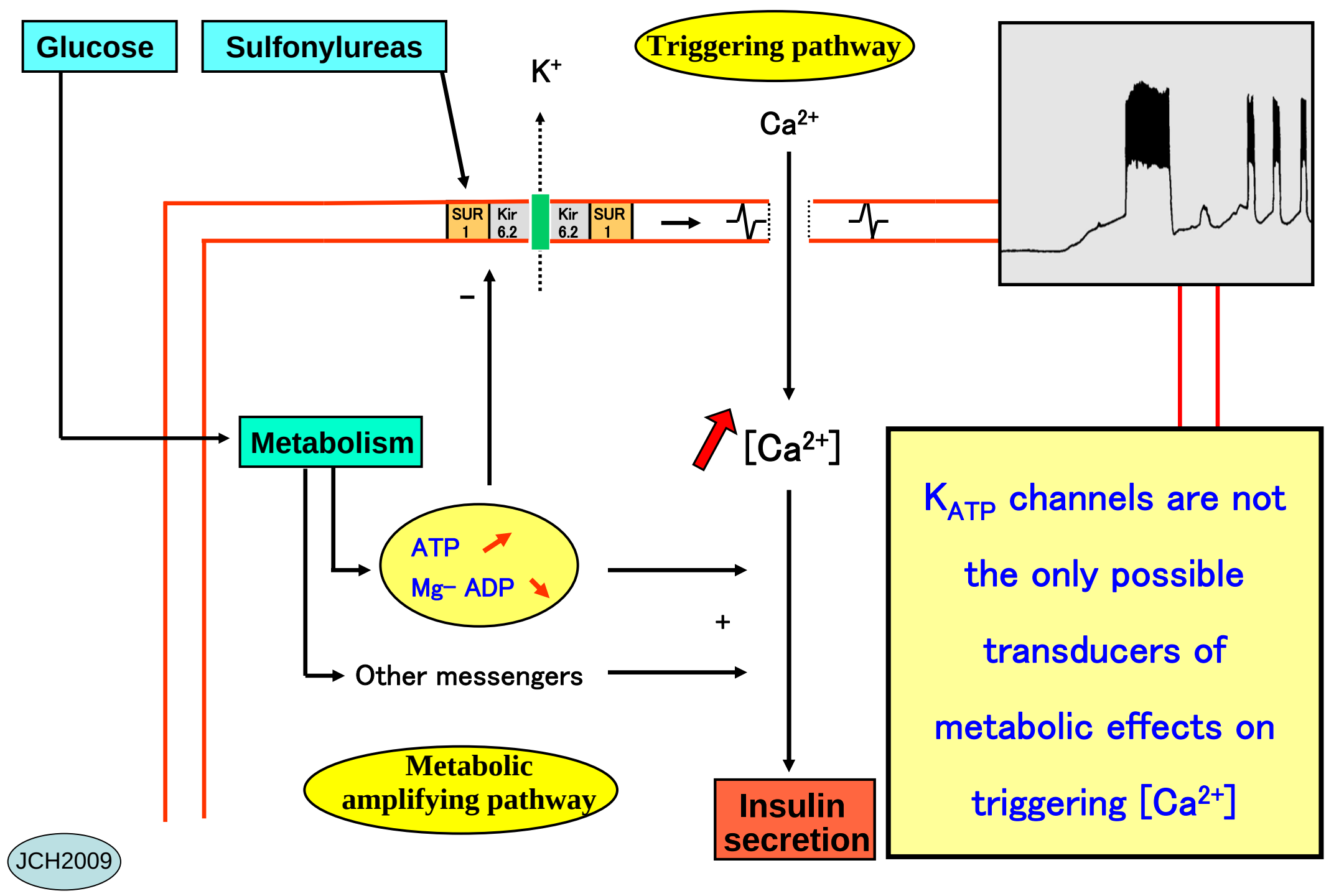


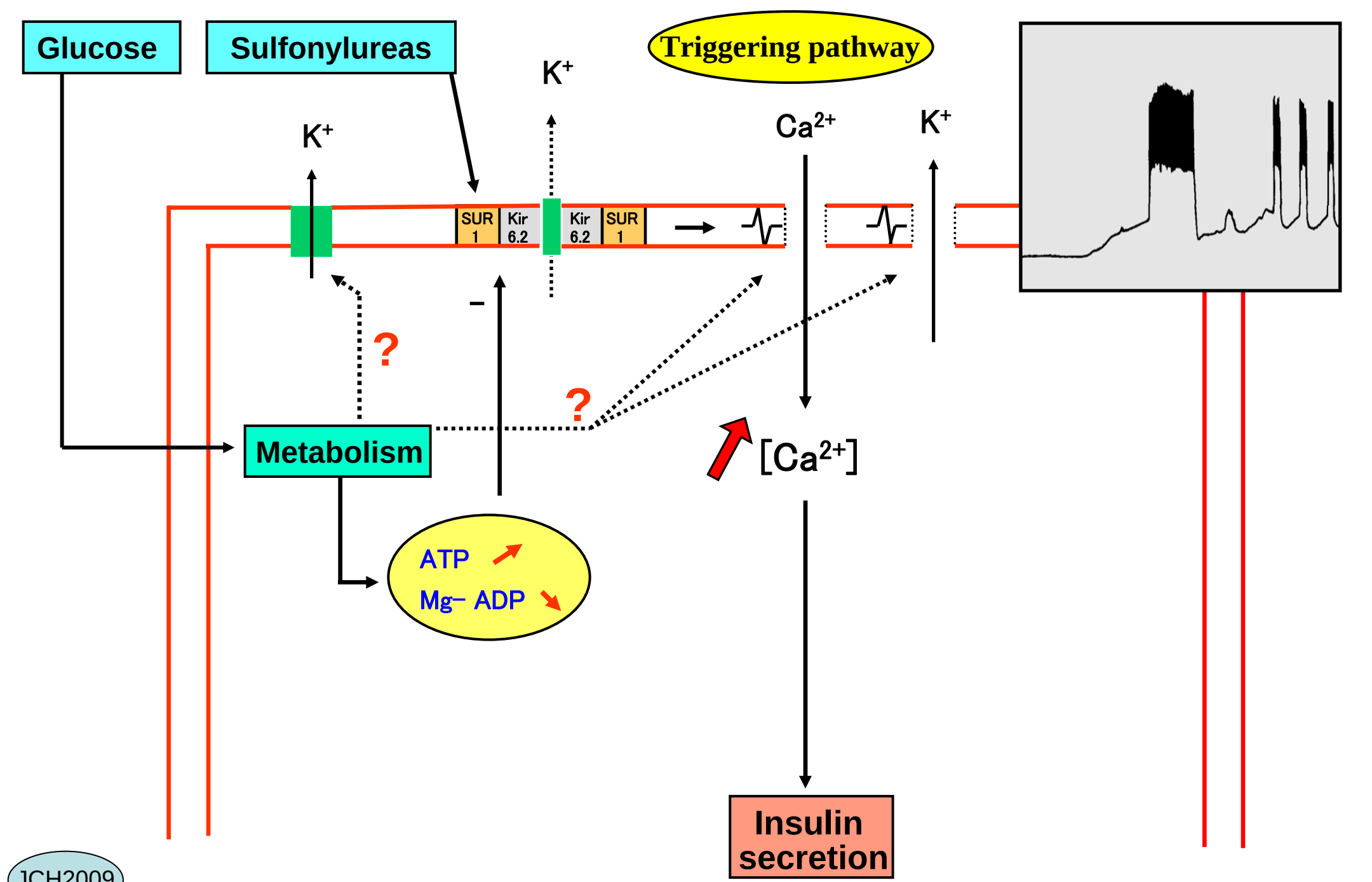
Glucose-induced biphasic responses in 2w-old islets cultured in 5 mM Glucose

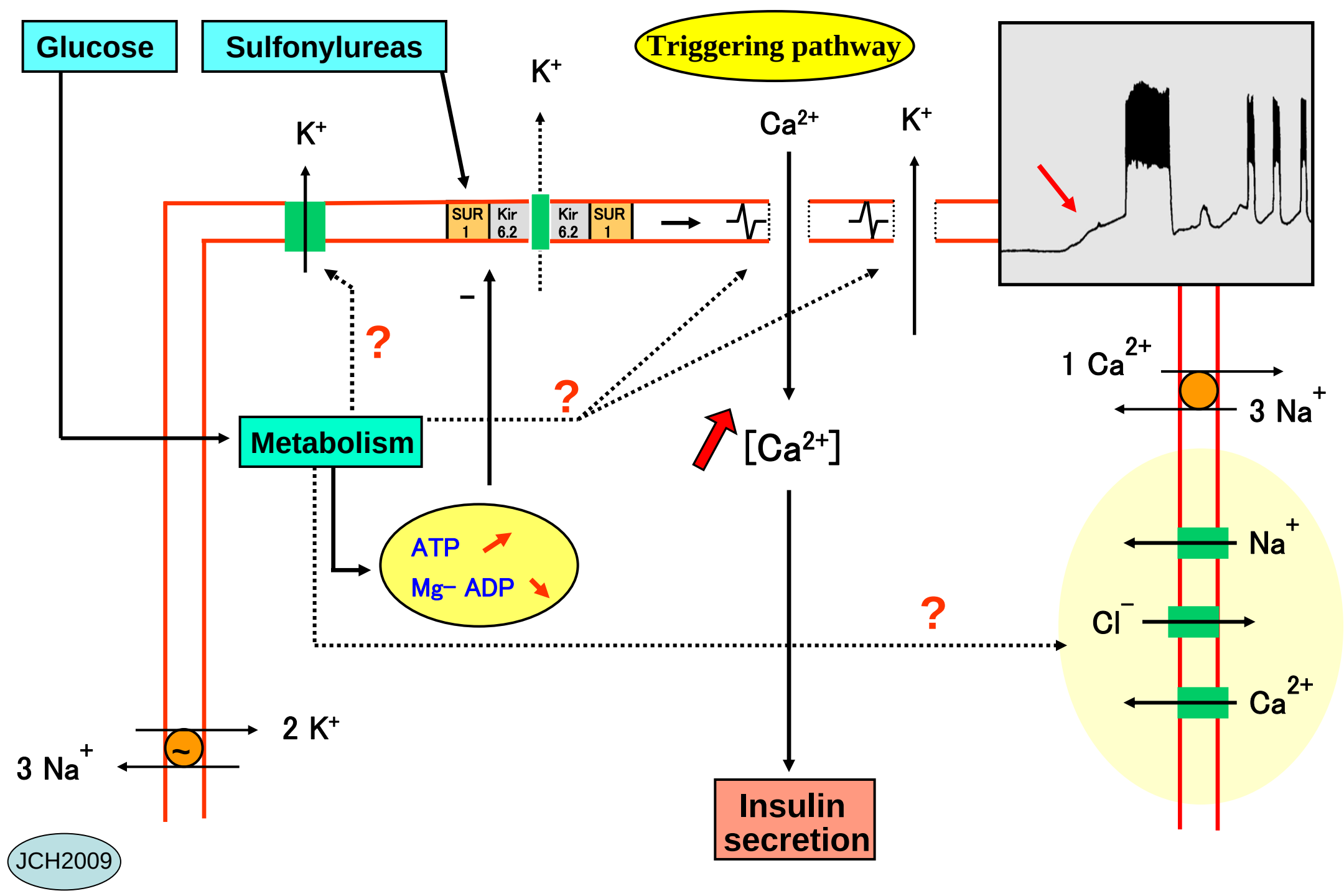


Glucose-induced biphasic responses in 2w-old islets cultured in 5 mM Glucose

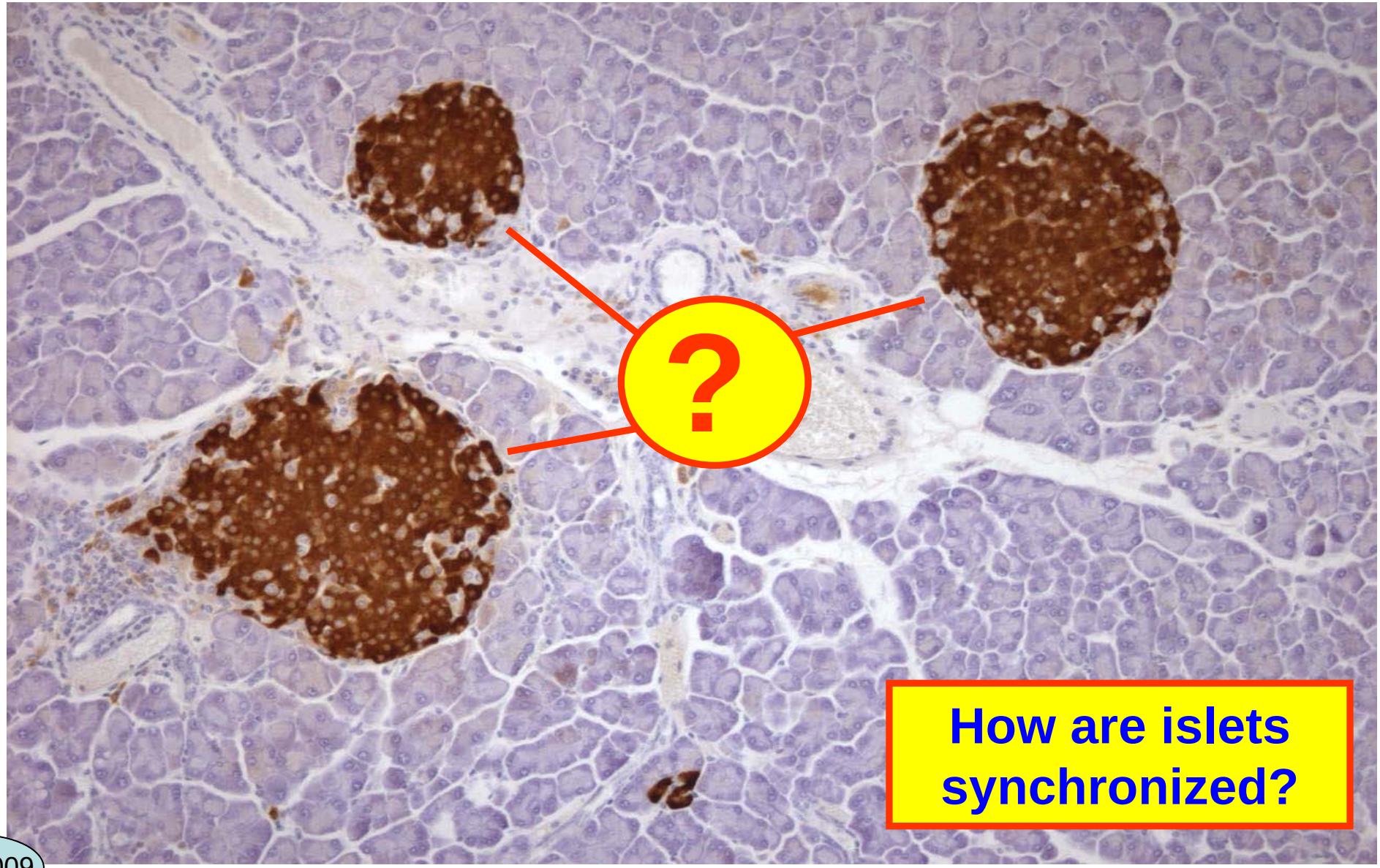



Glucose
Sulfonylureas
K+
Triggering pathway
Ca2+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
–
Metabolism
[Ca2+]
ATP
Mg– ADP
+
Other messengers
Metabolic amplifying pathway
Insulin secretion
KATP channels are not the only possible transducers of metabolic effects on triggering [Ca2+]
JCH2009


Glucose
Sulfonylureas
Triggering pathway
K+
K+
Ca2+
K+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
?
?
Metabolism
[Ca2+]
ATP
Mg– ADP
Insulin secretion
JCH2009


Glucose
Sulfonylureas
Triggering pathway
K+
K+
Ca2+
K+
SUR 1
Kir 6.2
Kir 6.2
SUR 1
?
?
Metabolism
ATP
Mg– ADP
[Ca2+]
1 Ca2+
3 Na+
Na+
Cl–
Ca2+
?
2 K+
3 Na+
Insulin secretion
JCH2009

Pulsatility of Insulin Secretion



JCH2009