



Lancet Diabetes & Endocrinology

医学TOP

CPU 一流期刊

ESI学科分类: 临床医学

简介

JCI 7.54

IF(5) 38.8

SCU 医学A-

SCI升级版 医学1区

SCI基础版 医学1区

SCI Q1

IF 44.5

CUG 医学T1

XJU 一区

Tuning of cellular insulin release by music for real-time diabetes control

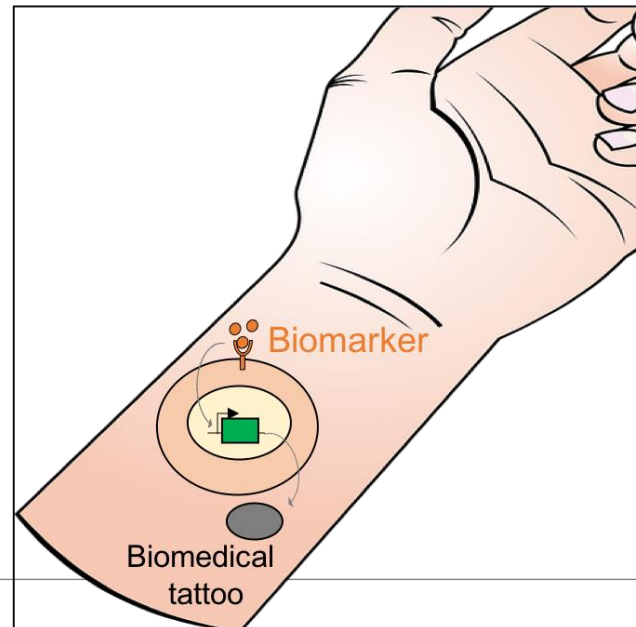
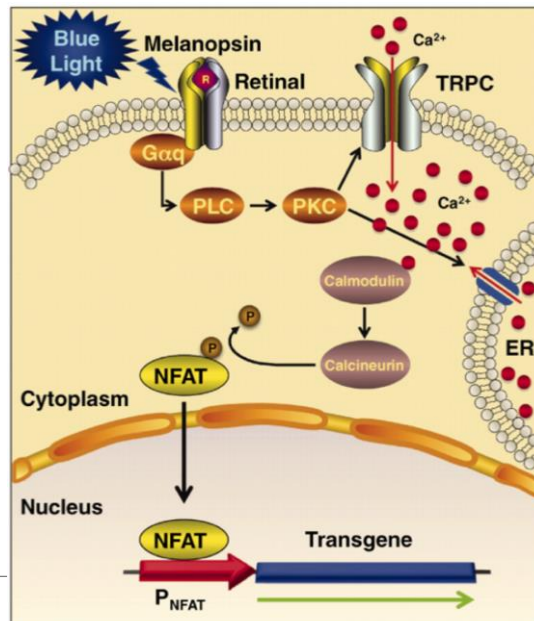
Presenter: Xiong Xiao

2024.03.31

Prof. Dr. Martin Fussenegger

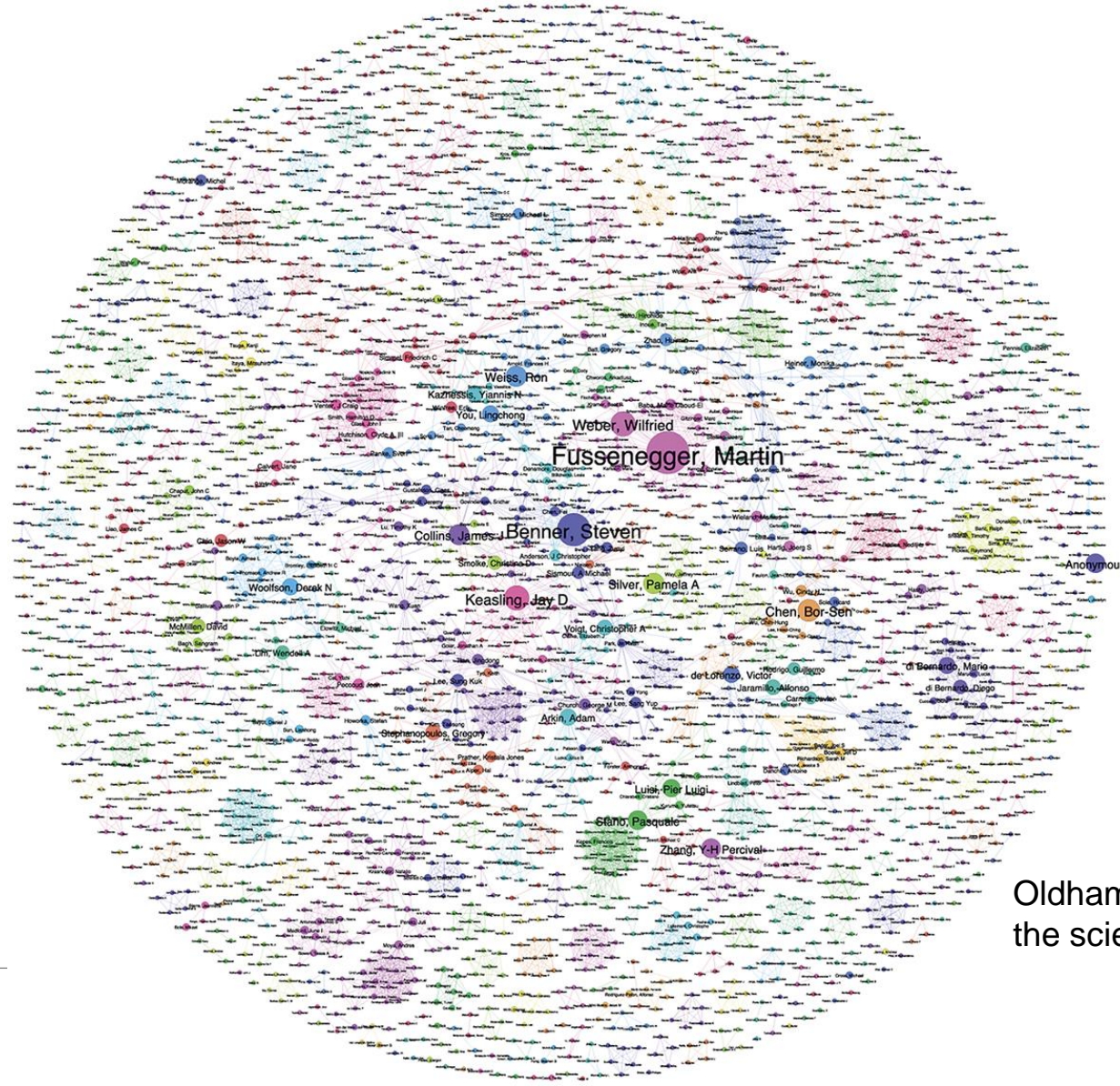
Full Professor at the Department of Biosystems Science and Engineering,
ETH Zürich

“Synthetic Biology: From Biotechnology to Human Therapy”



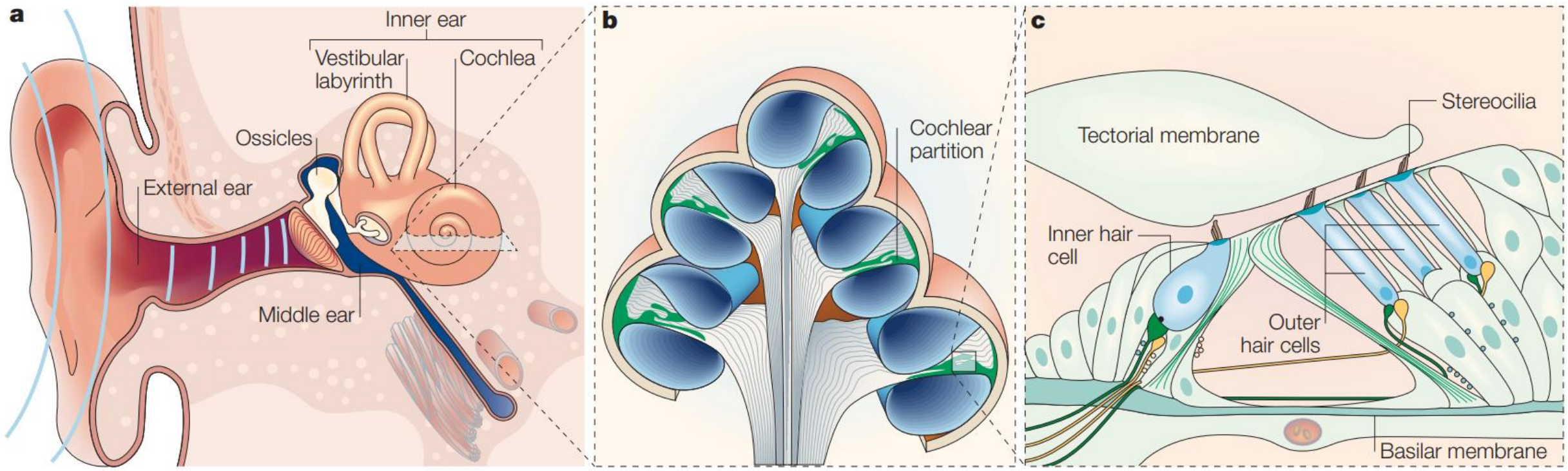
Retrieved from:
<https://bsse.ethz.ch/research/research-groups/biotechnology-and-bioengineering.html>

About the Author

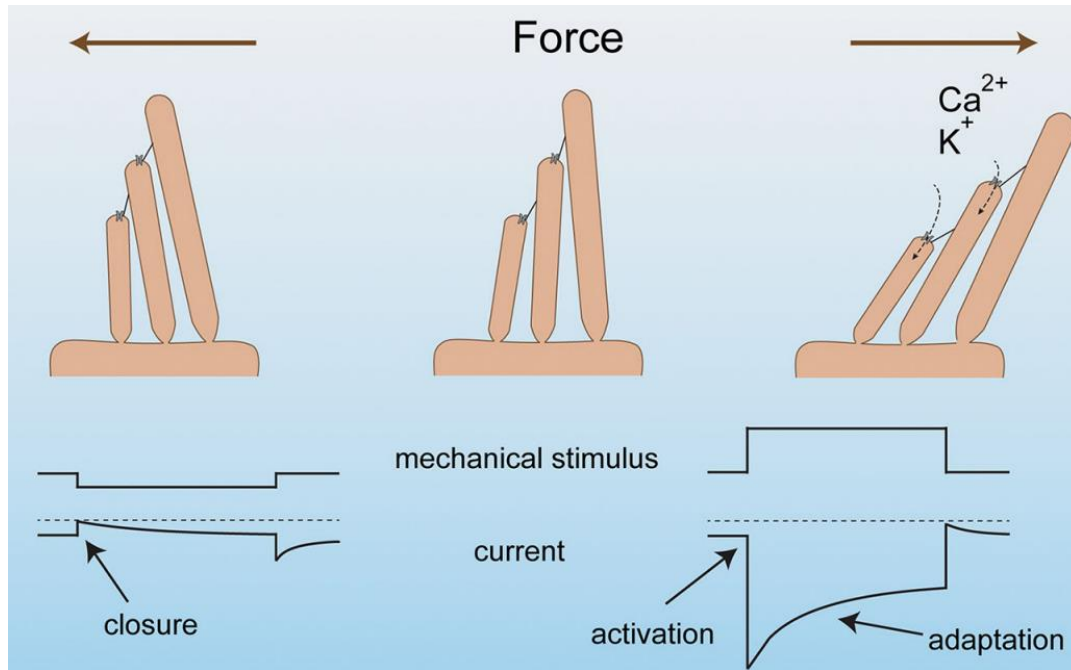


Oldham et al. 2012. Synthetic biology: mapping the scientific landscape. PLoS One, 7(4) e34368

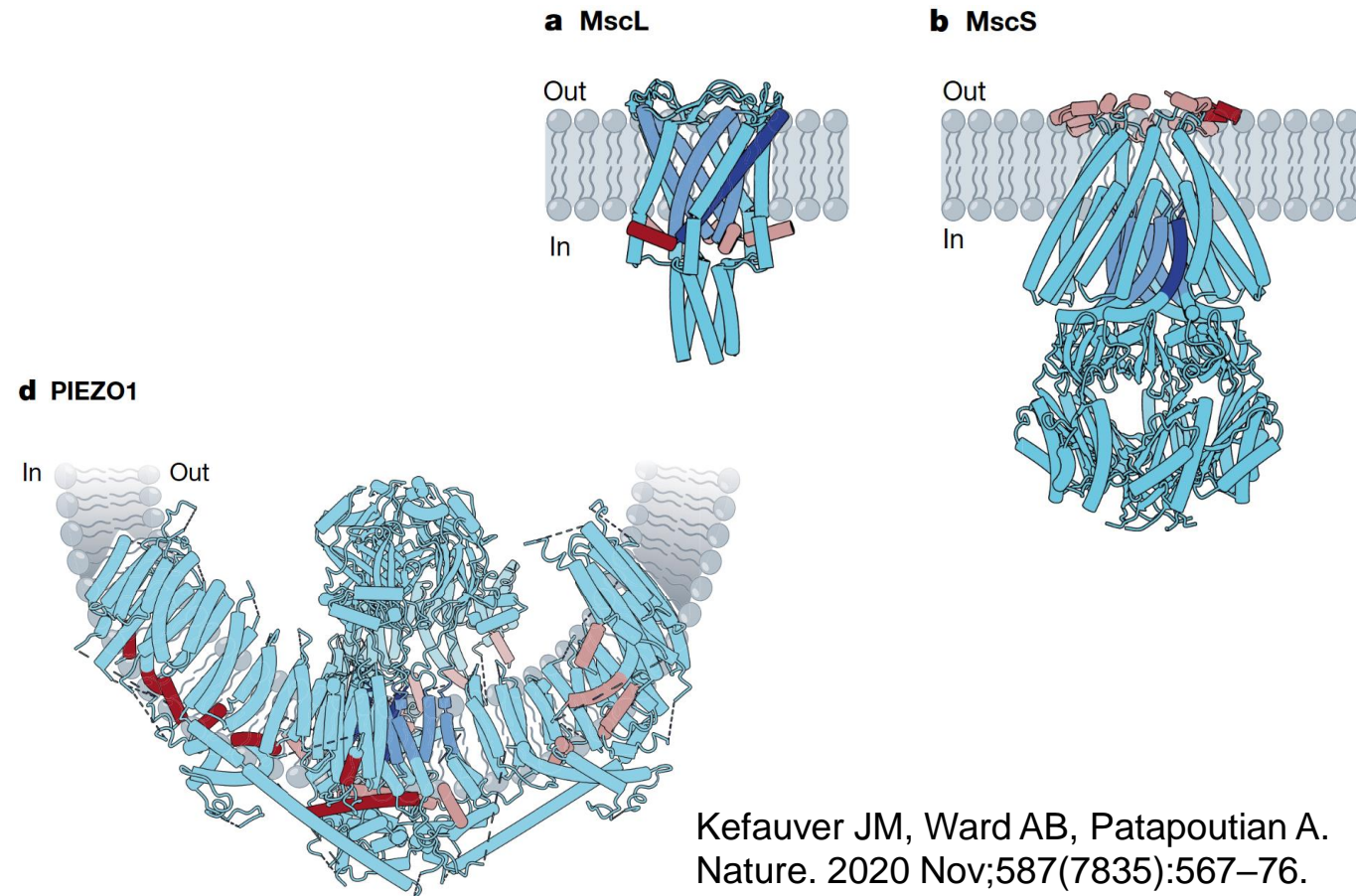
Music consists of acoustic waves that are converted by the bony ossicles in the middle ear into mechanical vibrations.



Mechanosensitive ion channels are ubiquitous across all kingdoms.

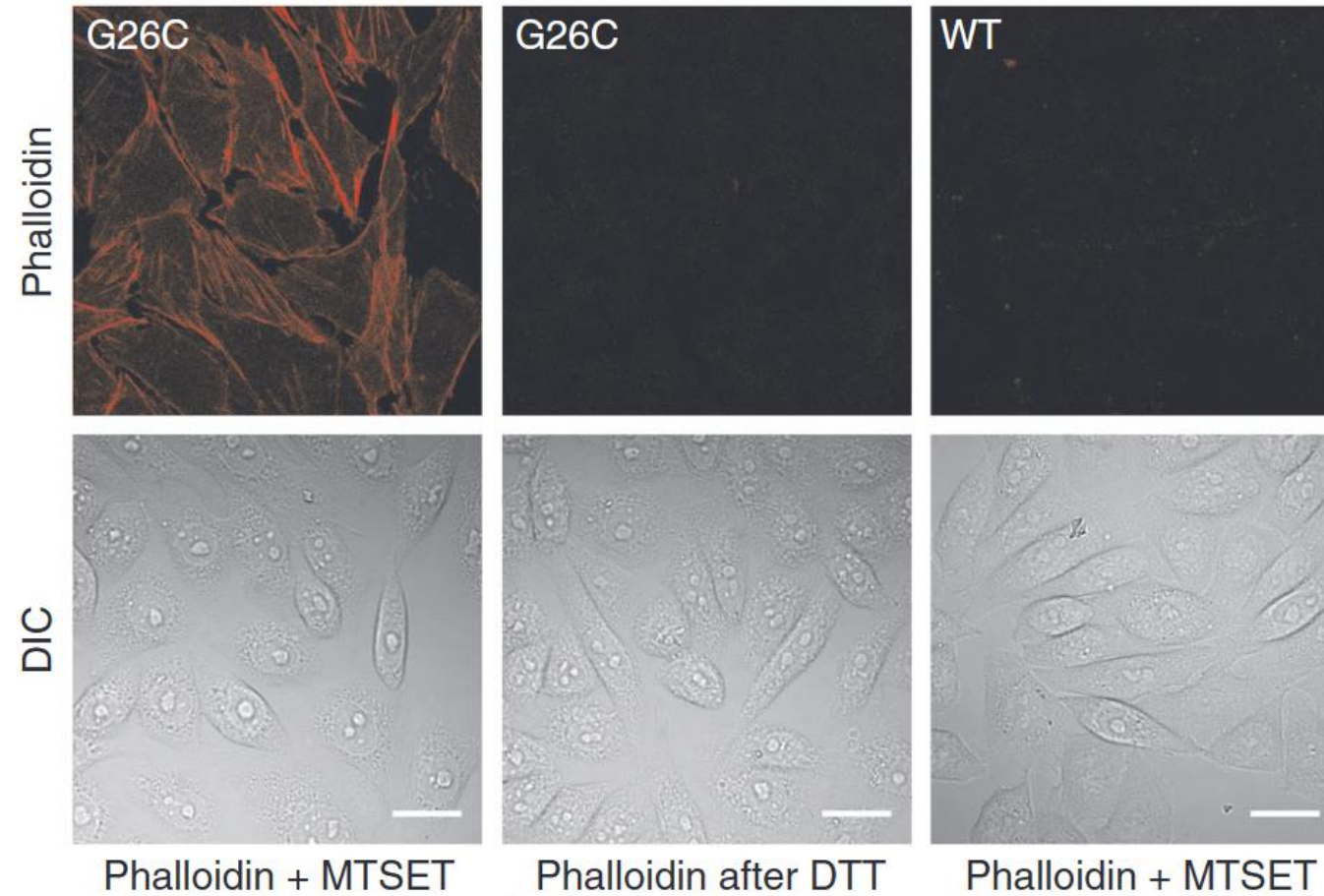


Qiu X, Müller U. Neuron. 2022 Nov 16;110(22):3667–87.



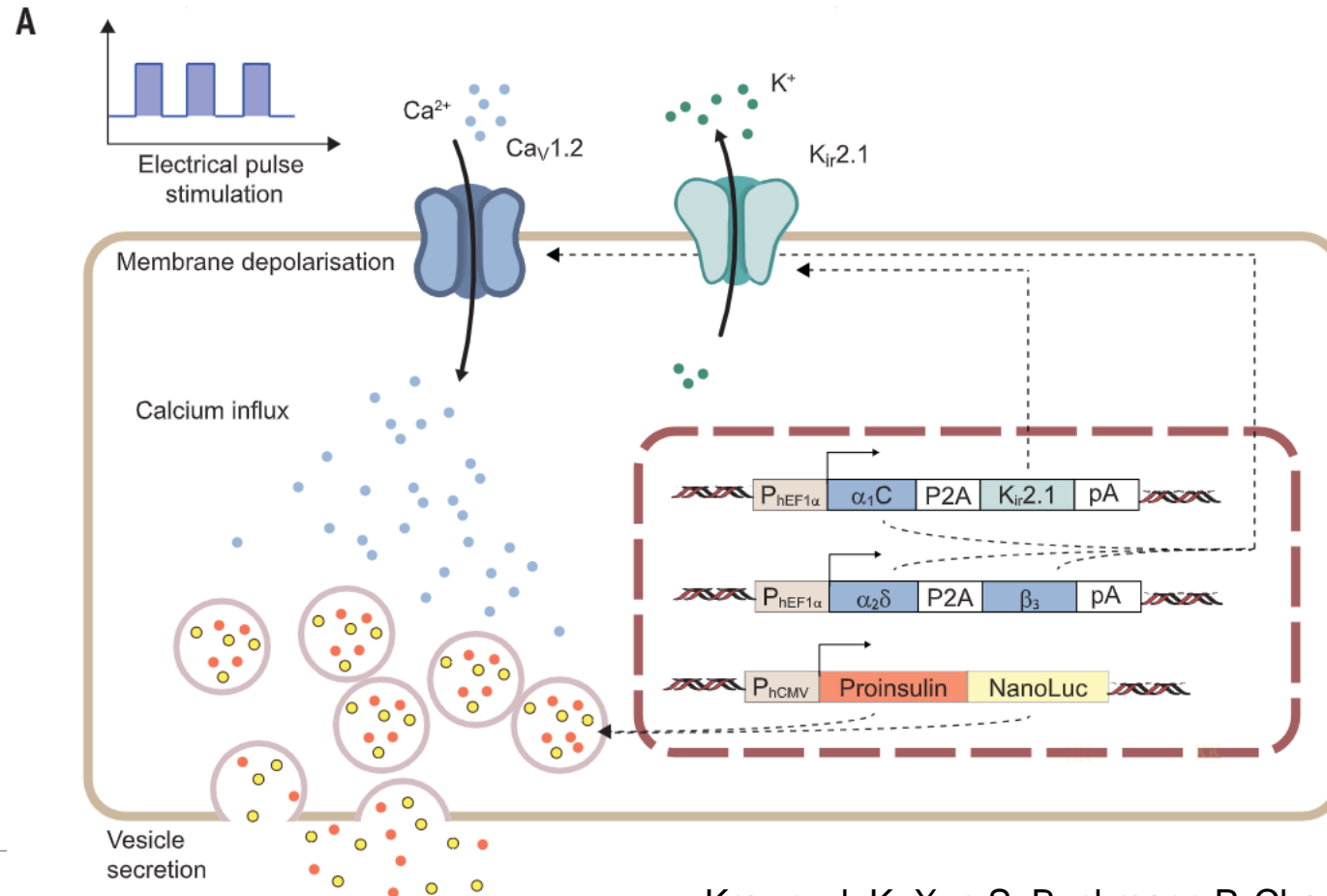
Kefauver JM, Ward AB, Patapoutian A.
 Nature. 2020 Nov;587(7835):567–76.

Modified *Escherichia coli* MscL has been expressed in mammalian cells.



Control

Many gene switches have been developed for use in next-generation cell-based therapies to treat multiple diseases.



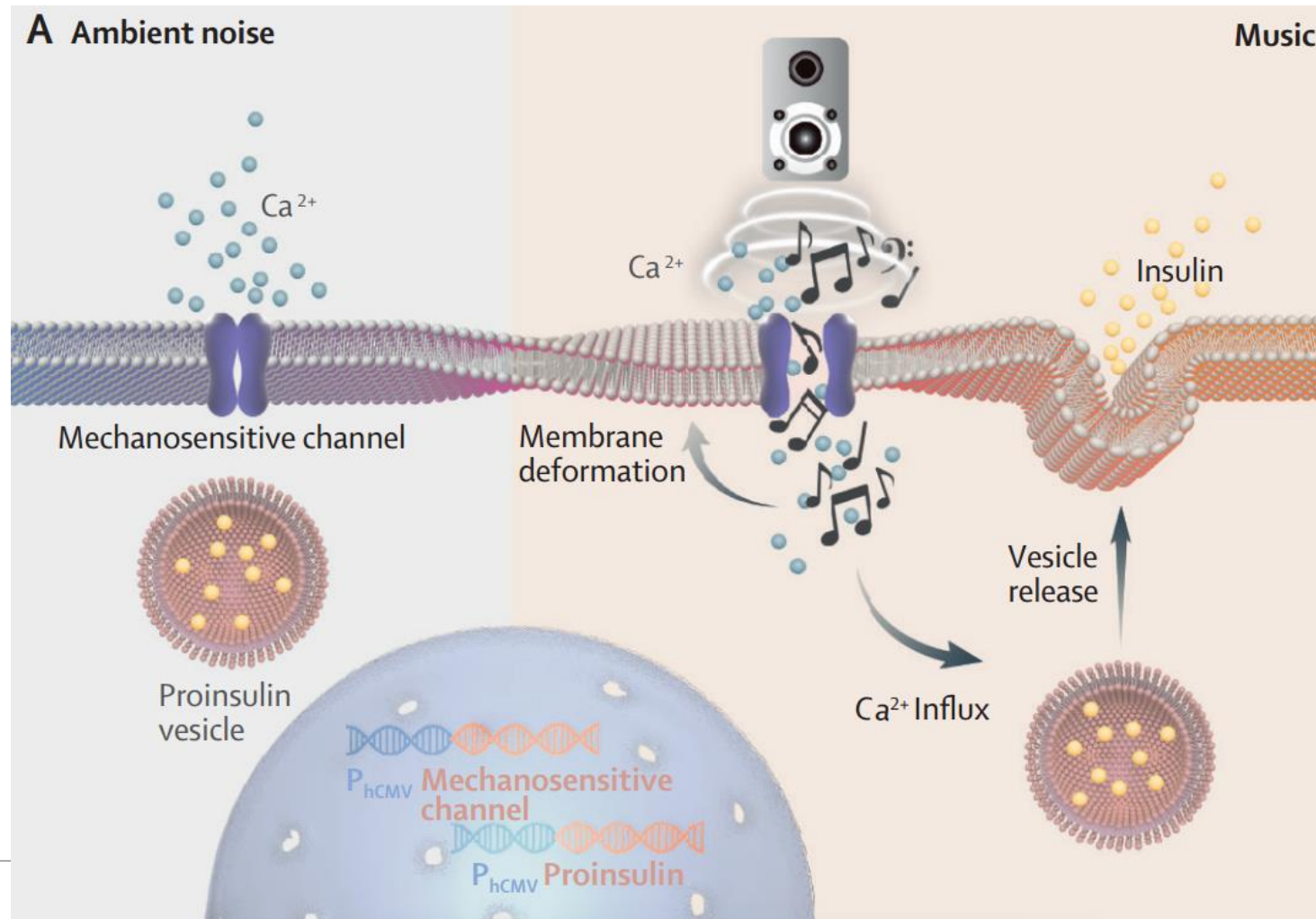
Systemic delivery faces **pharmacokinetic** challenges.

Traceless triggers, such as light, ultrasound, magnetic fields, radio waves, electricity, and heat, also face various challenges.

Thus, there is still a need for new switching modalities. . .

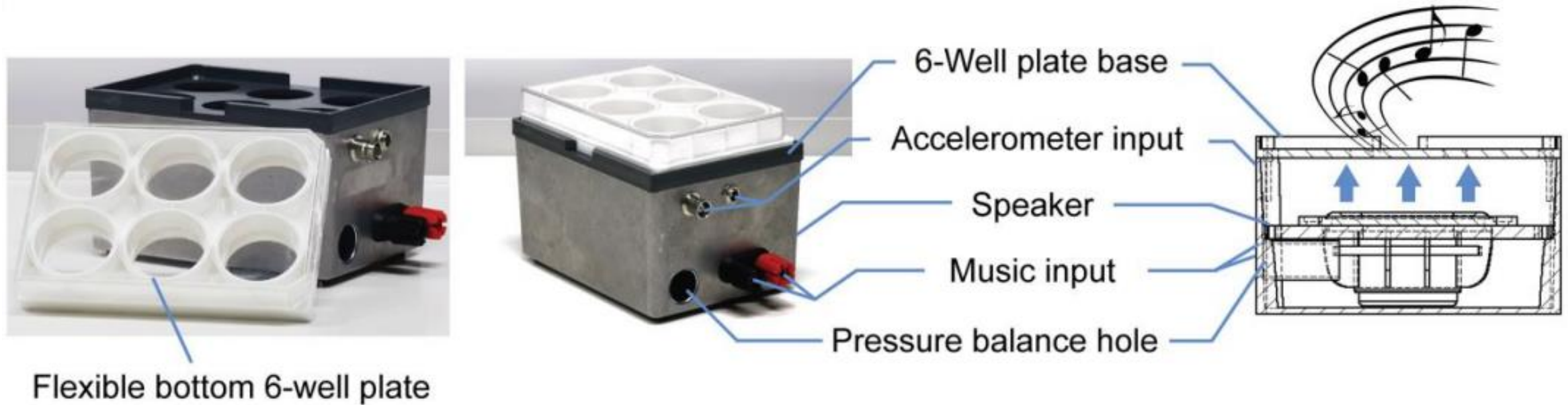
(Zhao et al. 2023)

Design of **Music**-Inducible Cellular **C**ontrol (MUSIC) system



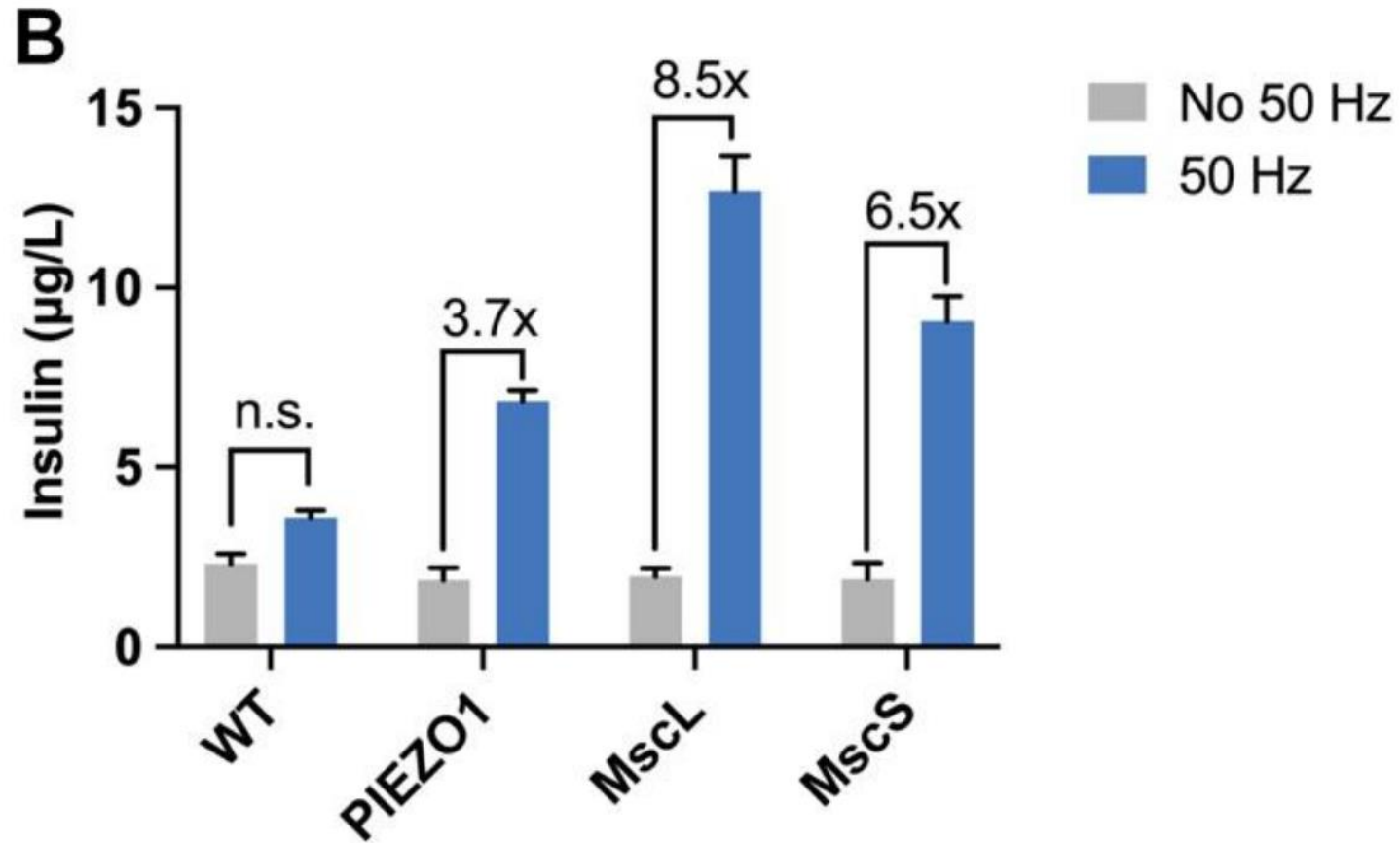
(Zhao et al. 2023)

Hardware & Devices



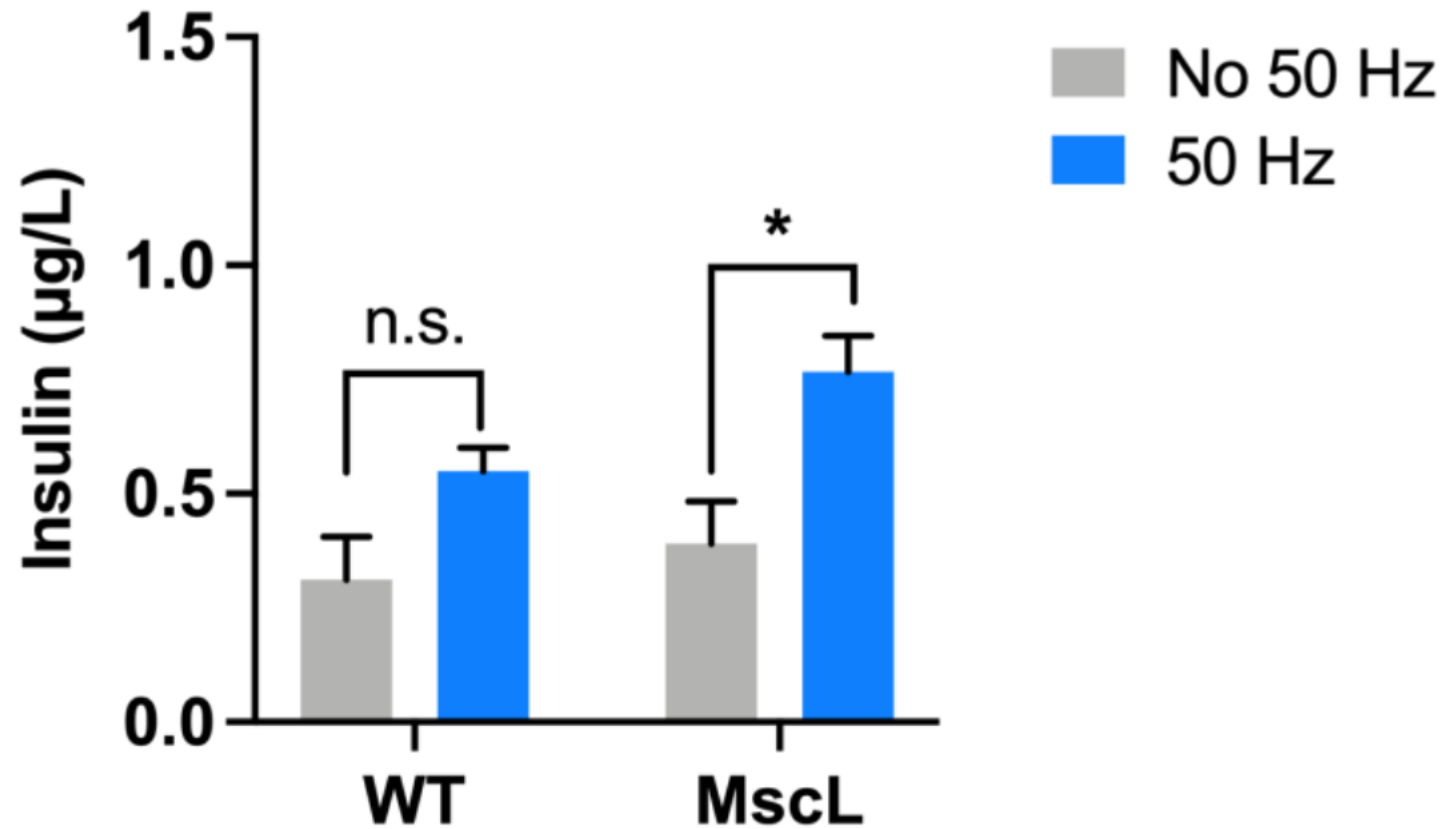
(Zhao et al. 2023)

Find the best channel



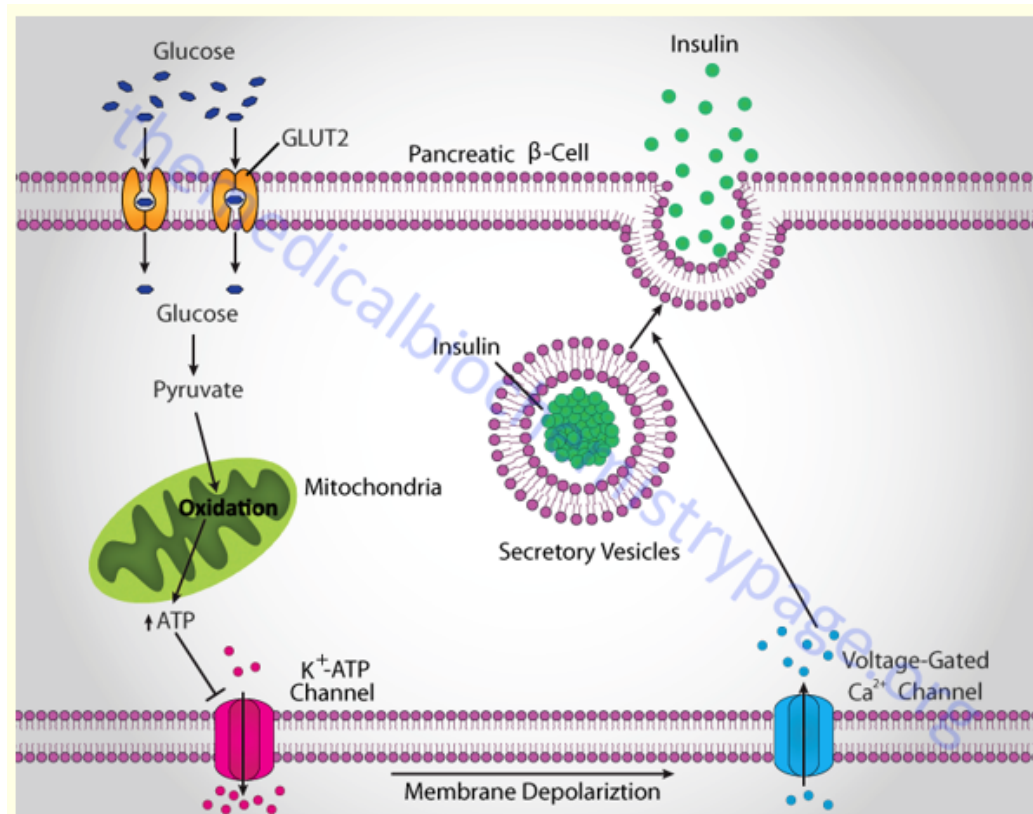
(Zhao et al. 2023)

Music-responsive cells need to be immobilised on the surface

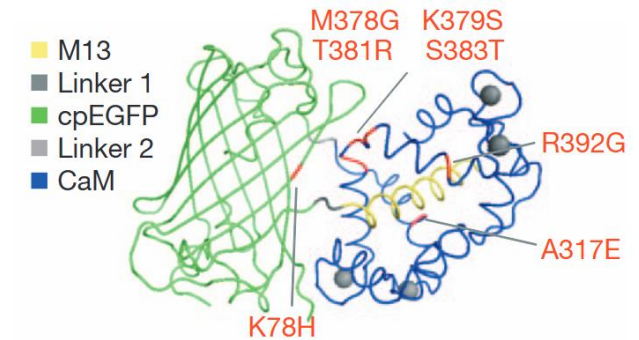
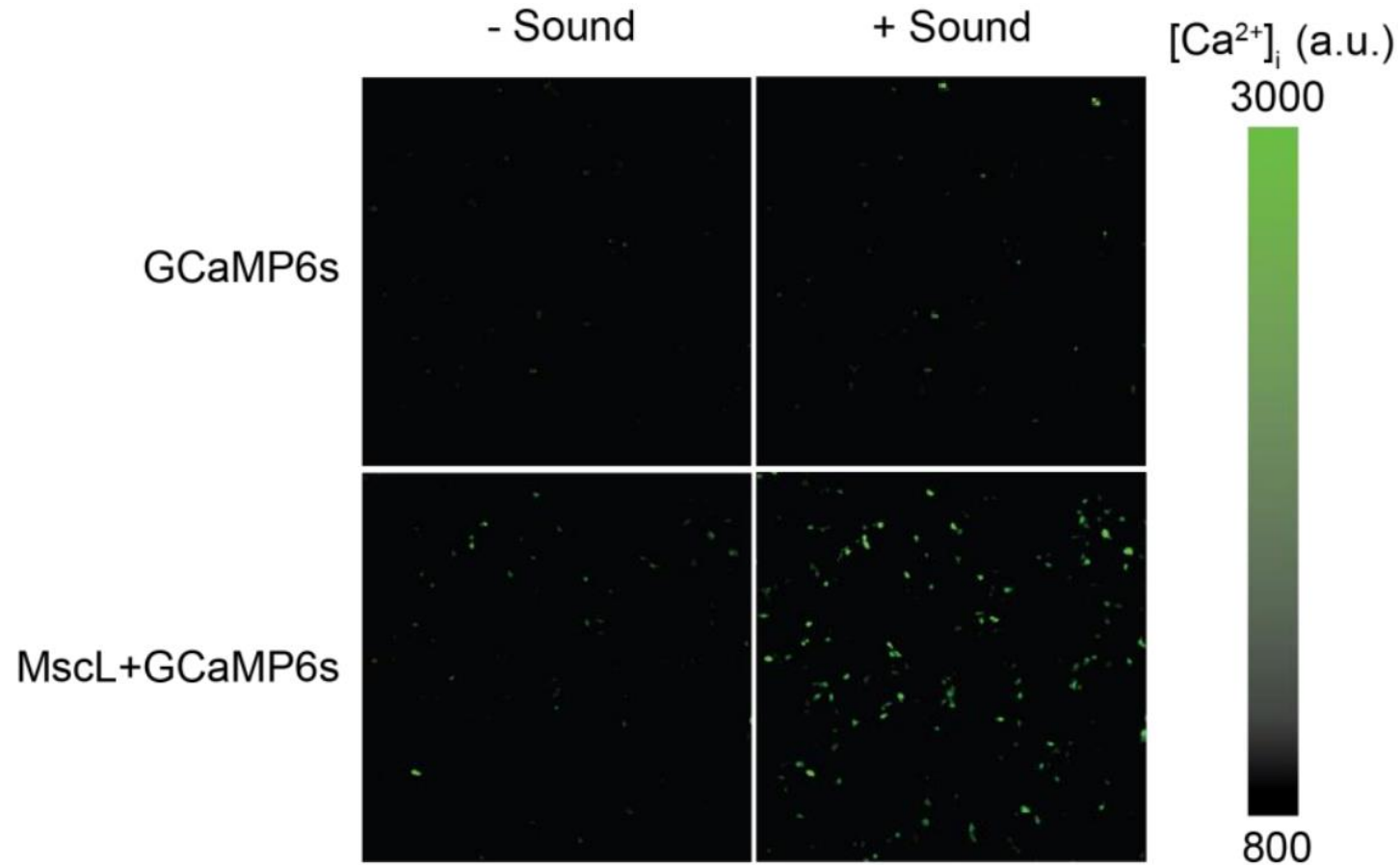


(Zhao et al. 2023)

The mechanistic connection between sound stimulation and insulin release by MUSIC_{INS} is likely to be mediated by **calcium**



The beta cells take up and catabolize glucose
 $\uparrow \rightarrow$ ATP levels $\uparrow \rightarrow$ closure of ATP-gated K^+ channels and depolarization of the plasma membrane $\uparrow \rightarrow$ cytosolic $[Ca^{2+}] \uparrow \rightarrow$ triggers exocytosis of insulin granules \uparrow .

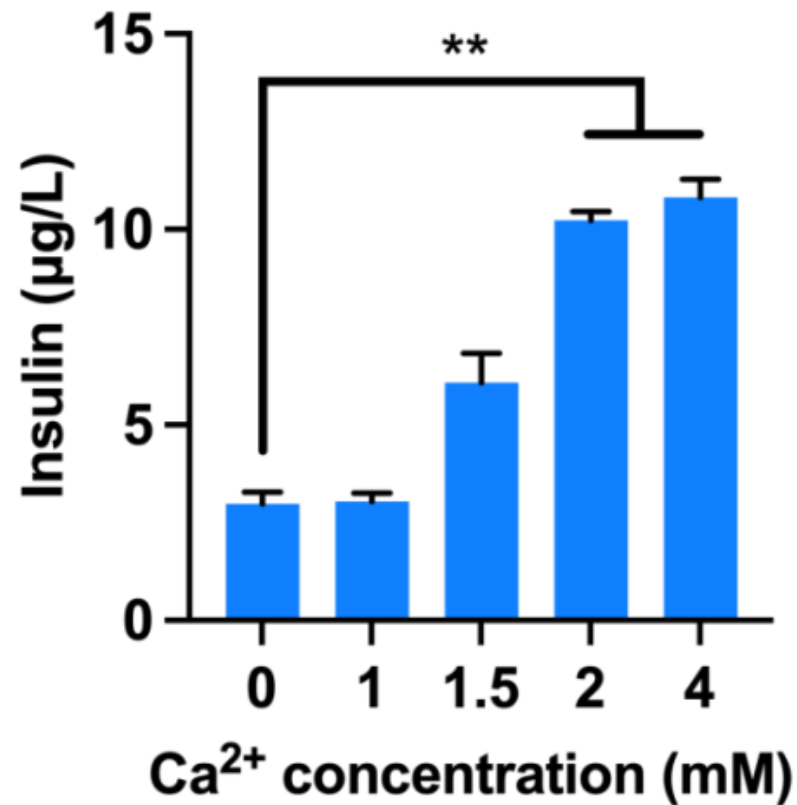
Imaging with fluorescent calcium indicator **GCaMP6s**

	cpEGFP	CaM
GCaMP5G	K78	A317 M378 K379 T381 S383 R392
GCaMP6s	K78H	T381R S383T R392G
GCaMP6m		M378G K379S T381R S383T R392G
GCaMP6f		A317E T381R S383T R392G

Chen TW et al. Nature. 2013 Jul
18;499(7458):295–300.

(Zhao et al. 2023)

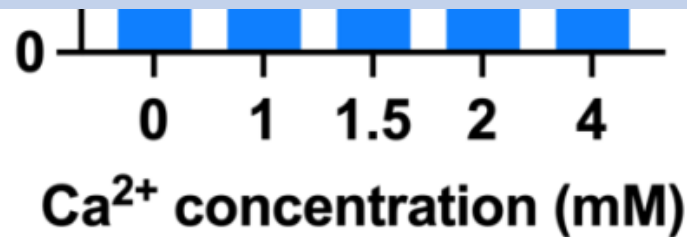
Sound-stimulated MUSIC_{INS} cells showed increased insulin release when incubated in higher calcium chloride concentrations



(Zhao et al. 2023)

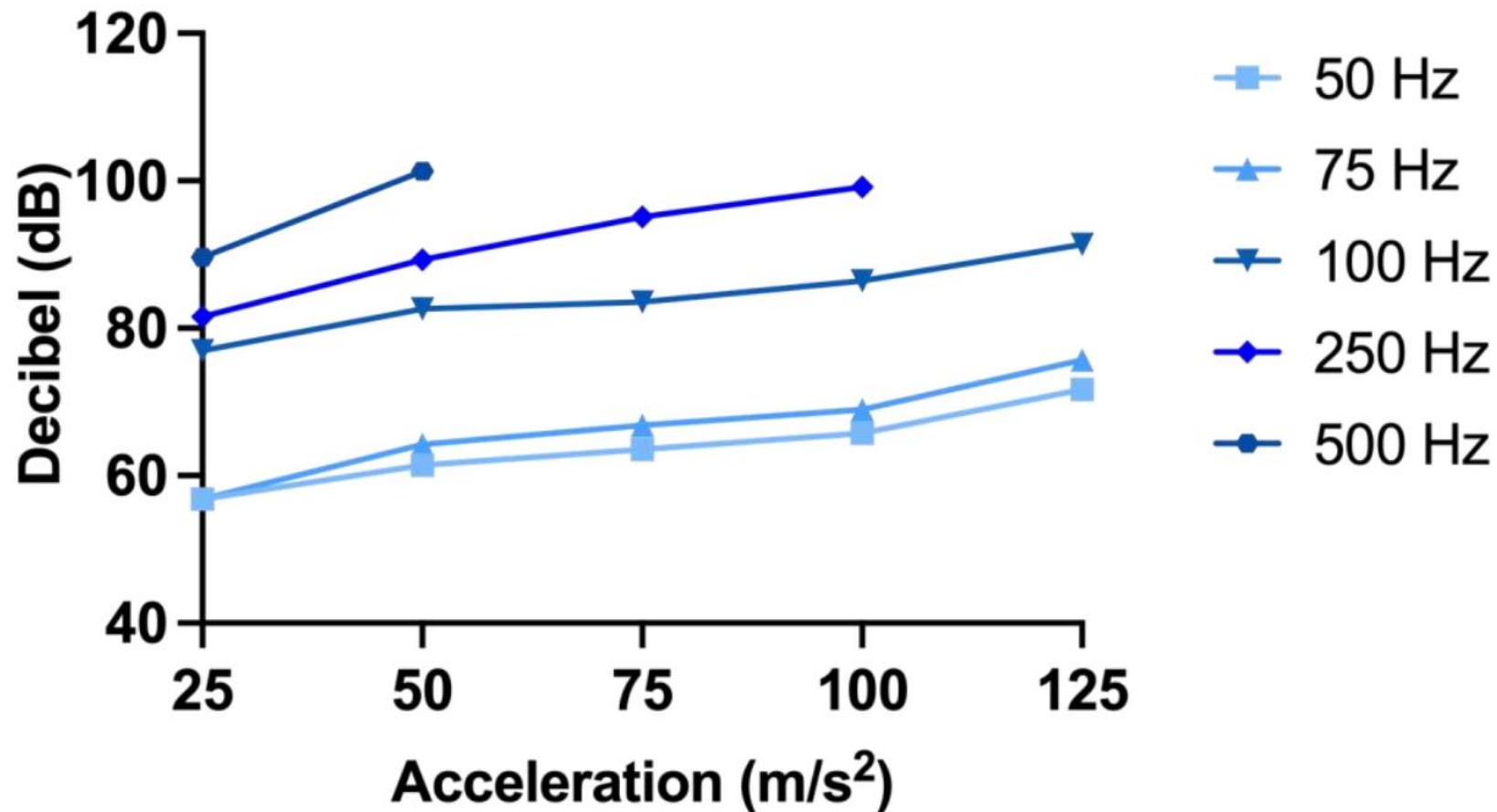
Sound-stimulated MUSIC_{INS} cells showed increased insulin release when incubated in higher calcium chloride concentrations

Taken together, these results support the idea that the sound waves act as mechanical forces to **open the MscL channels** and **initiate calcium influx**.



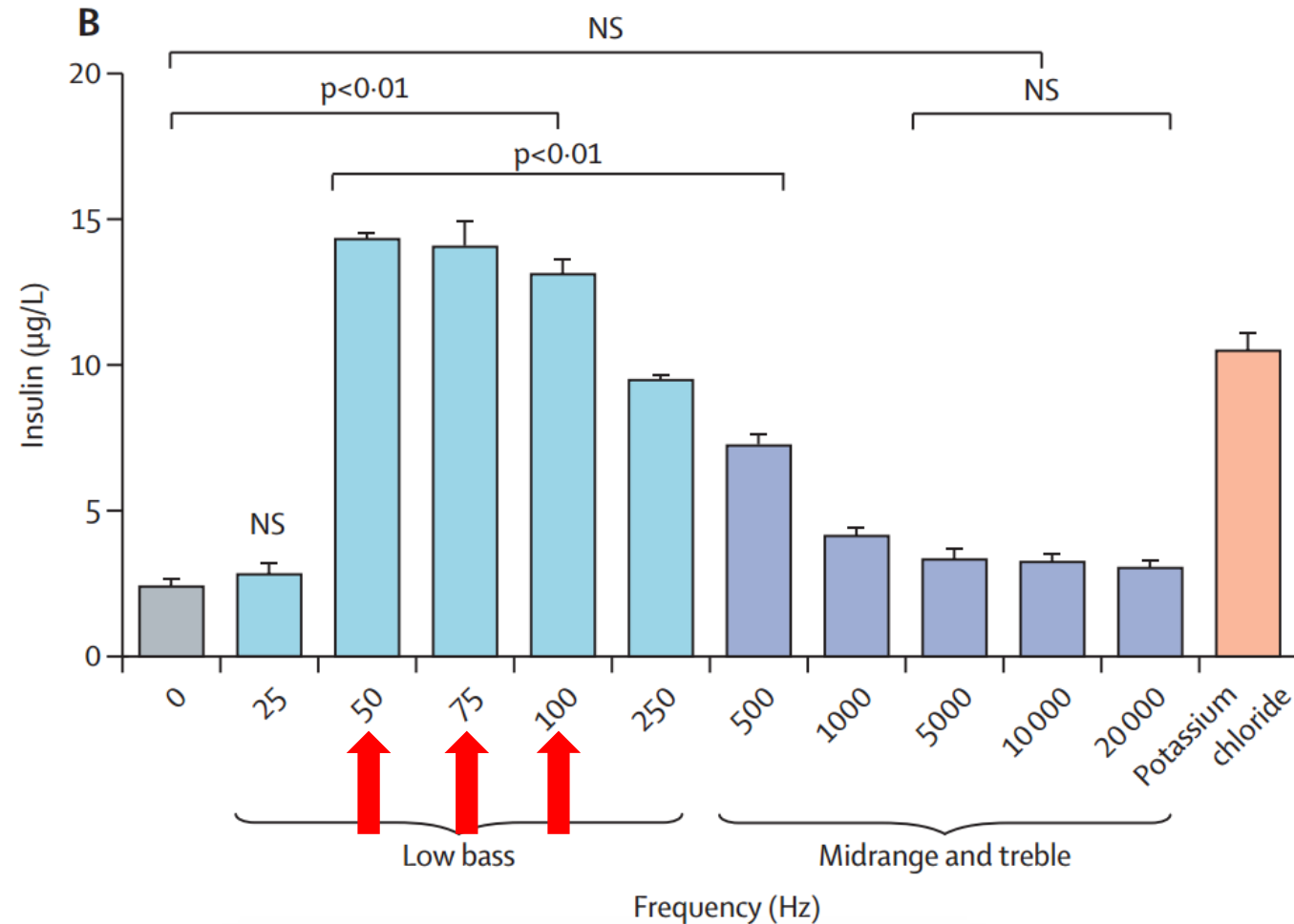
(Zhao et al. 2023)

Correlation of sound intensity and acceleration generated by the speaker setup



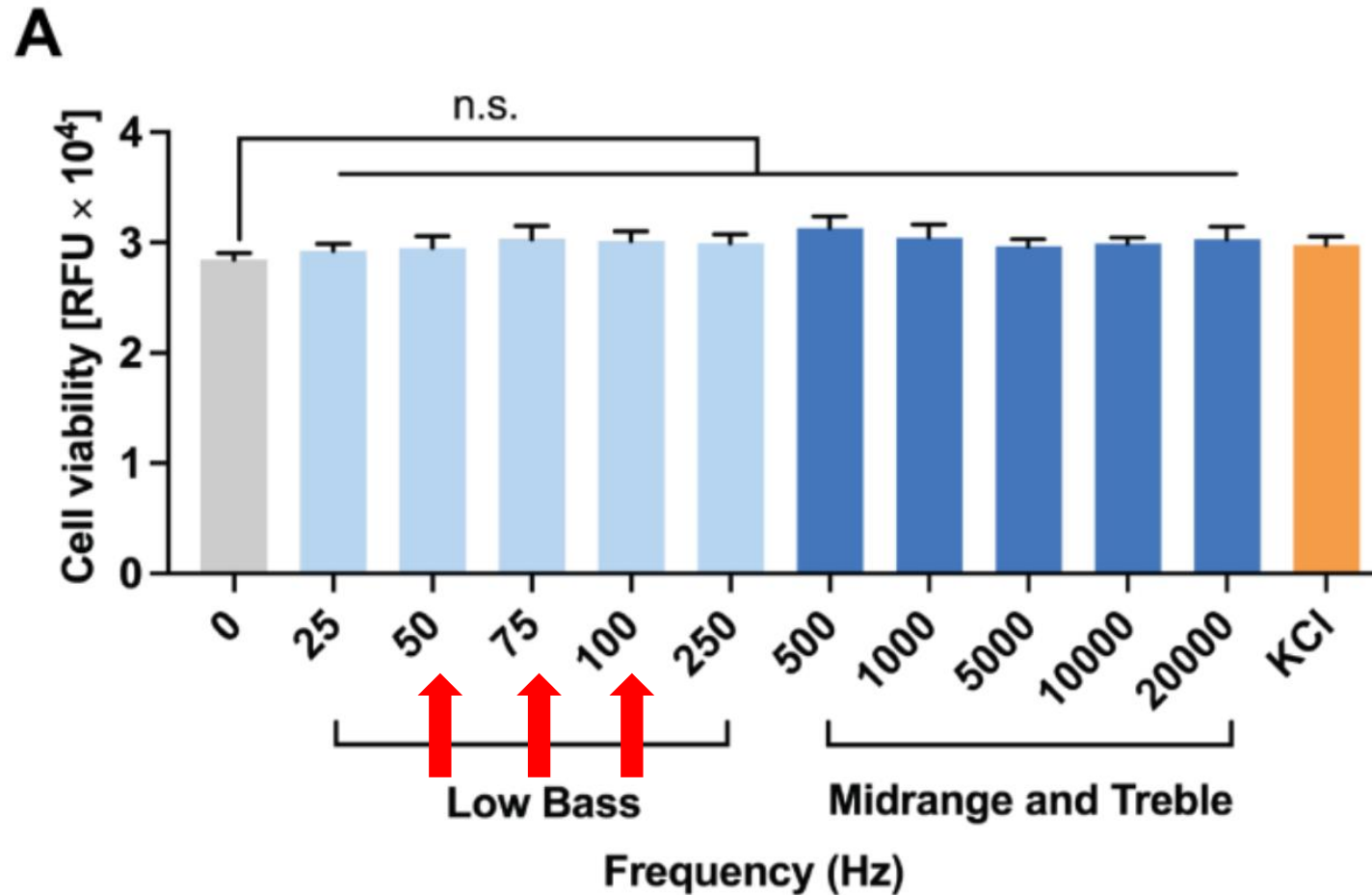
(Zhao et al. 2023)

Profile vesicular insulin release



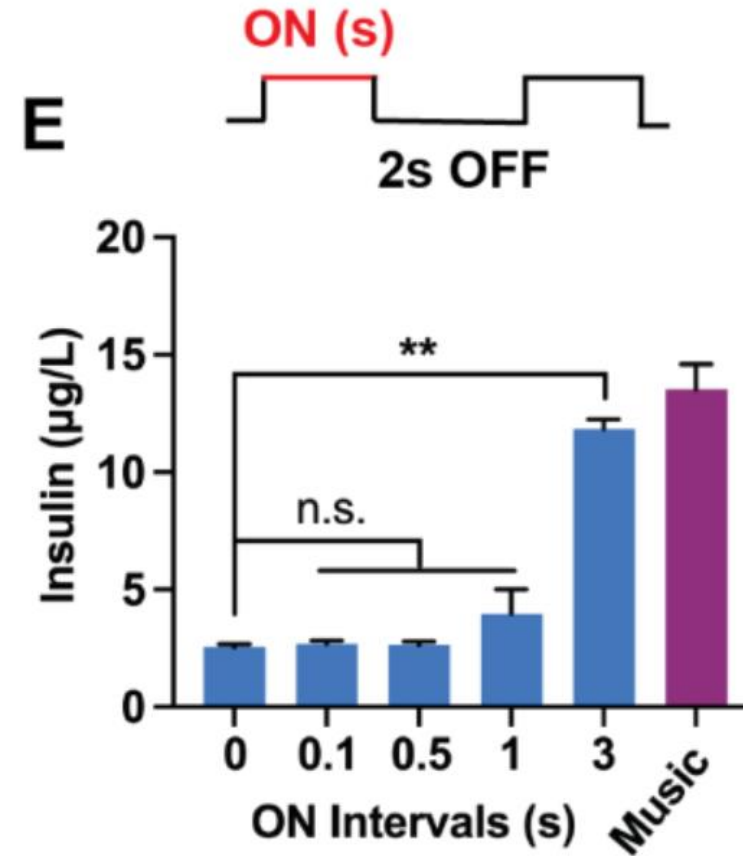
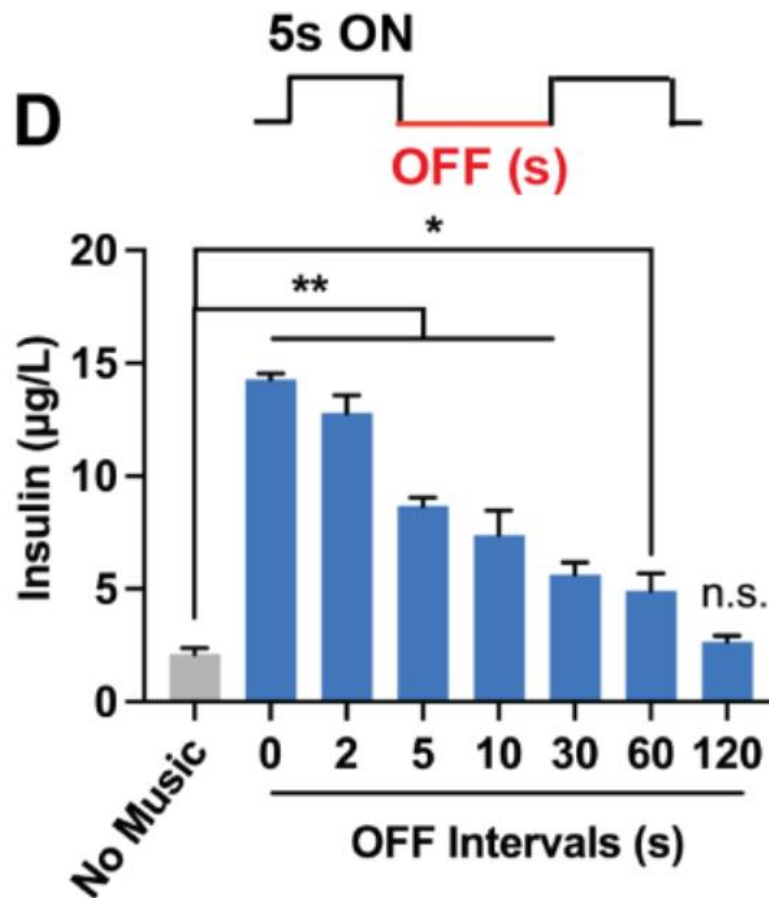
(Zhao et al. 2023)

Viability is not affected



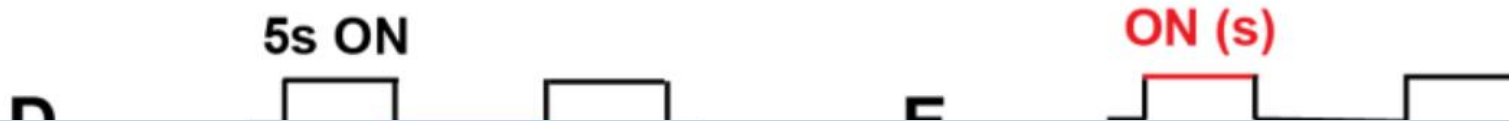
(Zhao et al. 2023)

Different sound programs

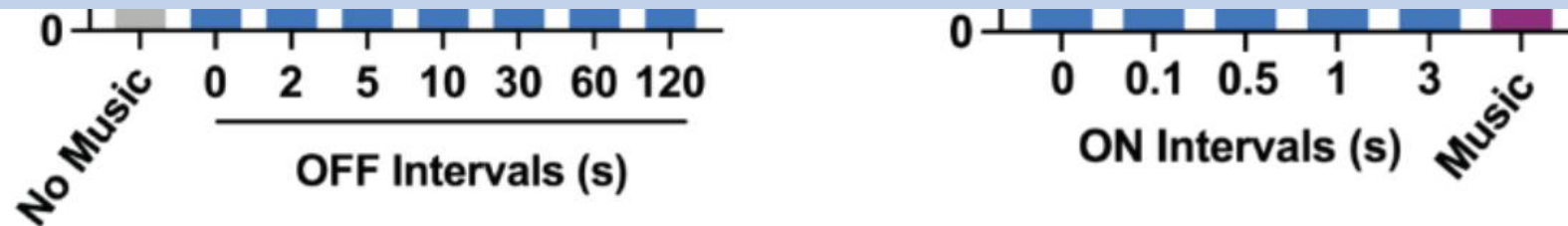


(Zhao et al. 2023)

Different sound programs

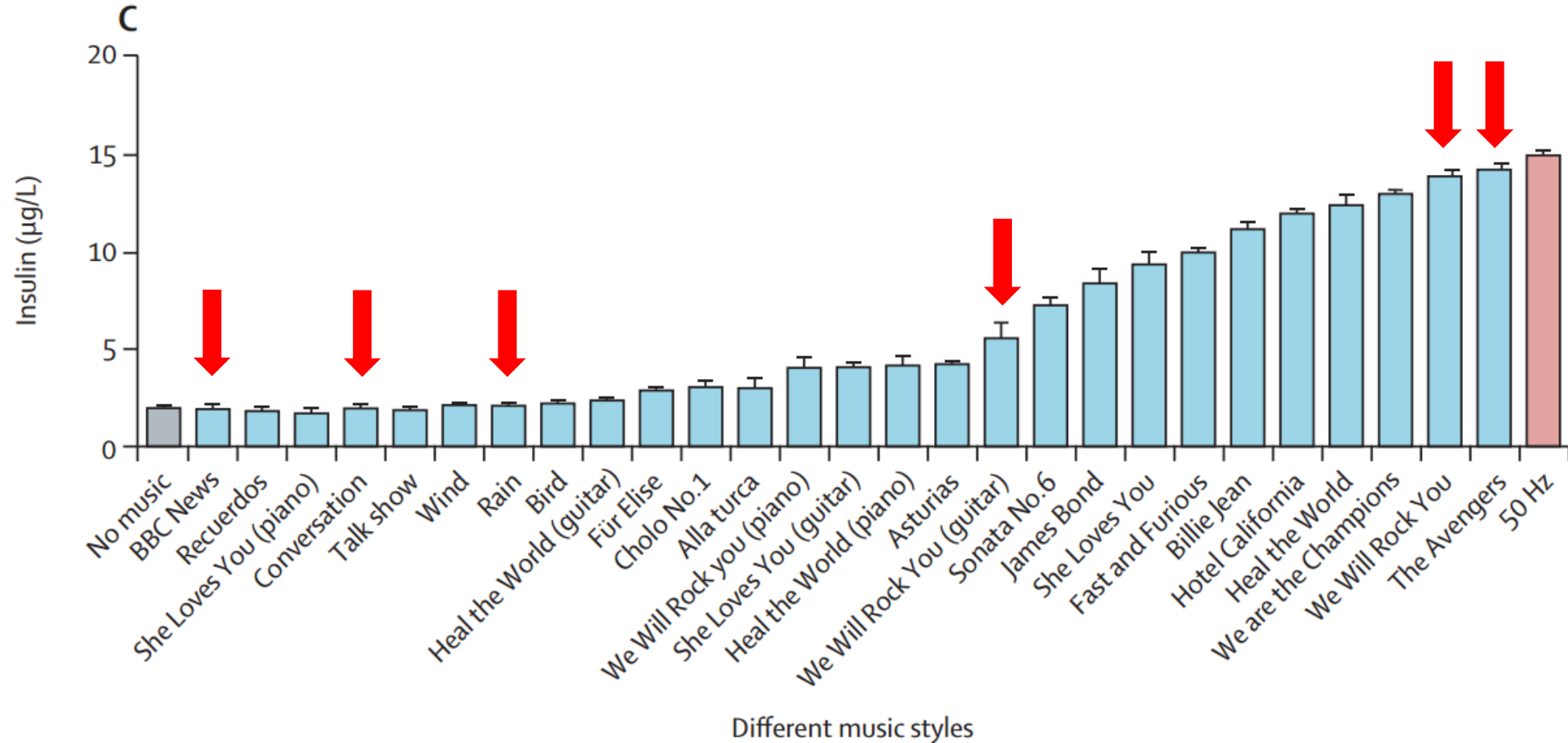


1. MUSIC_{INS} cells showed **maximum viability** while providing the **highest insulin release at 50 Hz & 60 dB**.
2. MUSIC activation requires at least **3 s of continuous music**.



(Zhao et al. 2023)

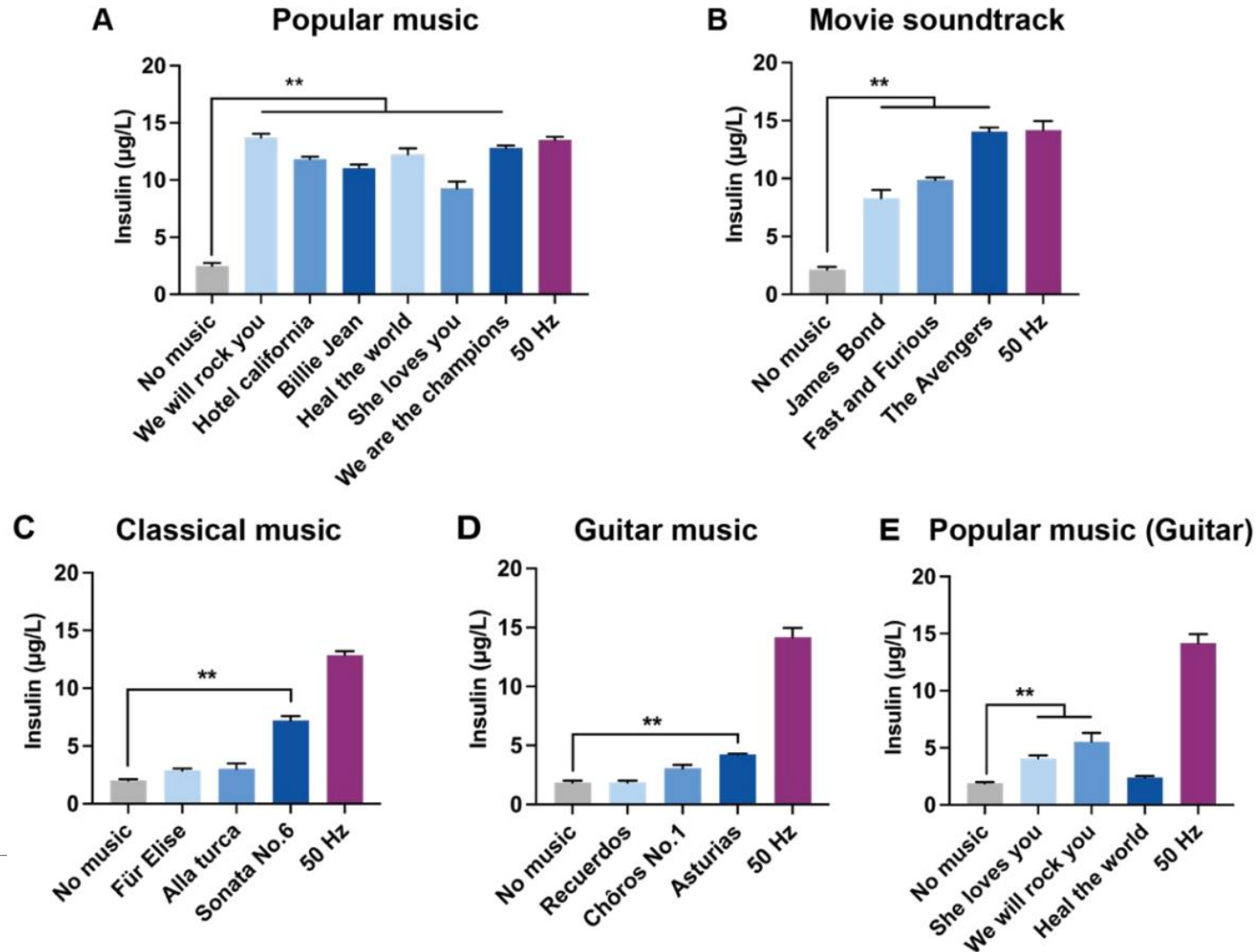
Different kinds of music



Part 3: Validation of insulin release performance to different musical genres

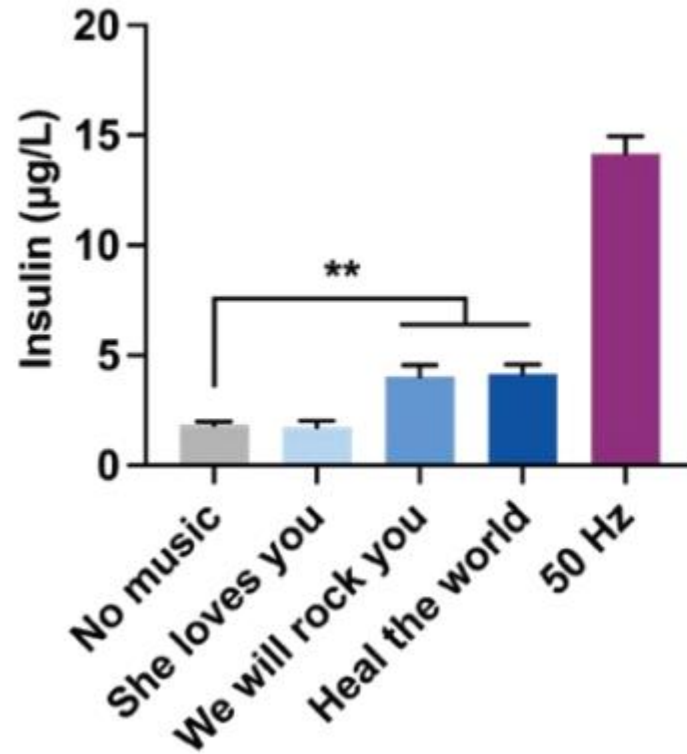


Responses to classical music and guitar music were more diverse

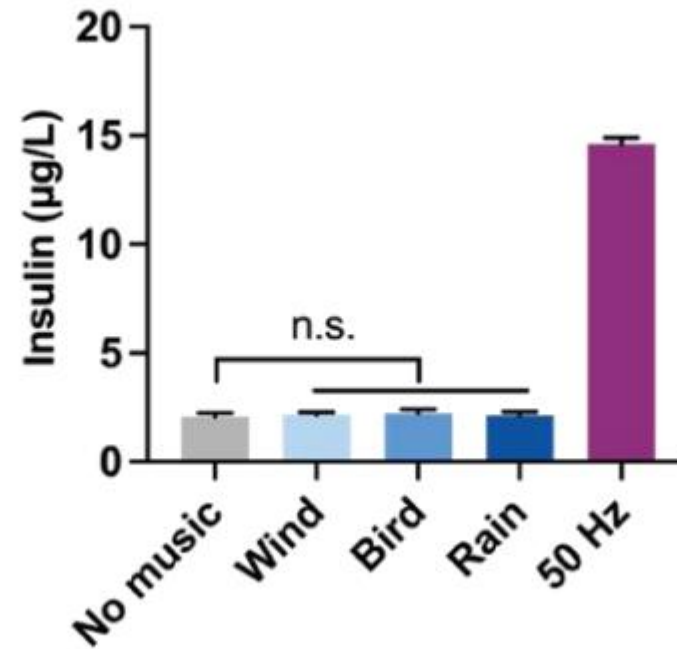


Environmental noises and speech did not trigger insulin release

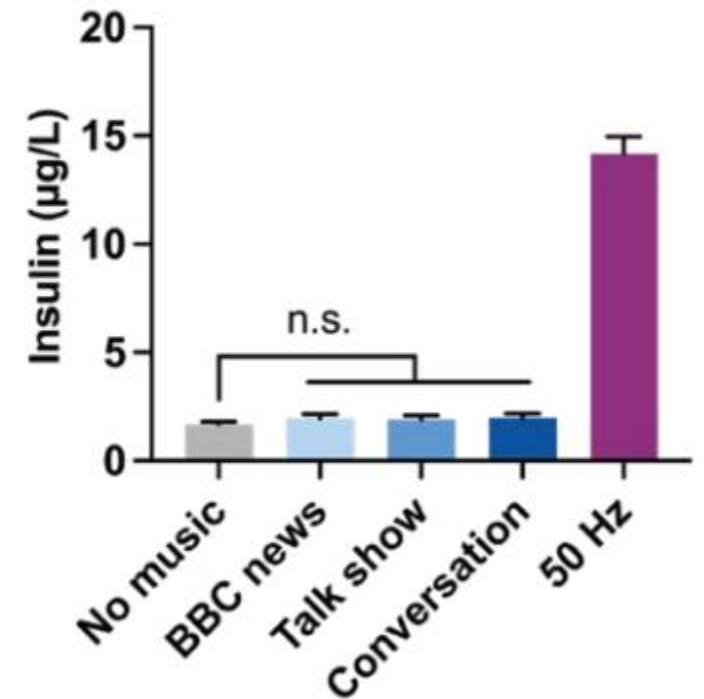
F Popular music (Piano)



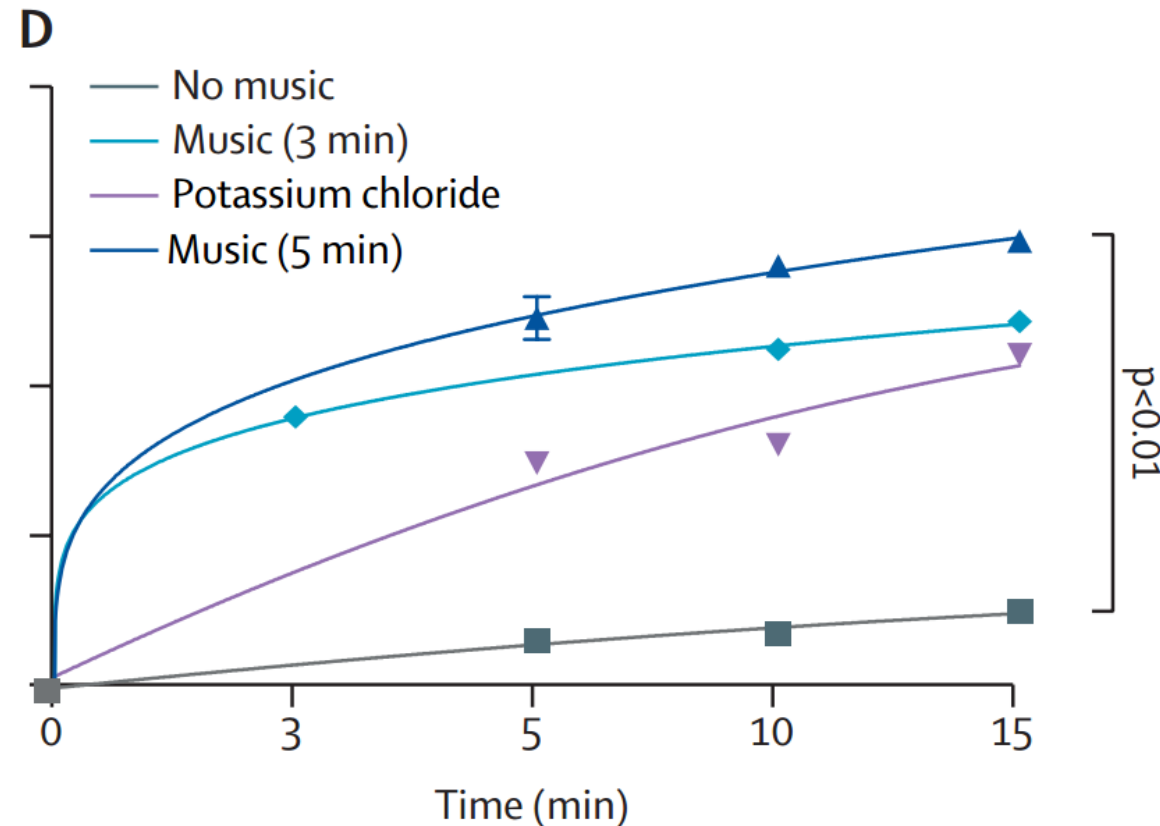
G Natural sounds



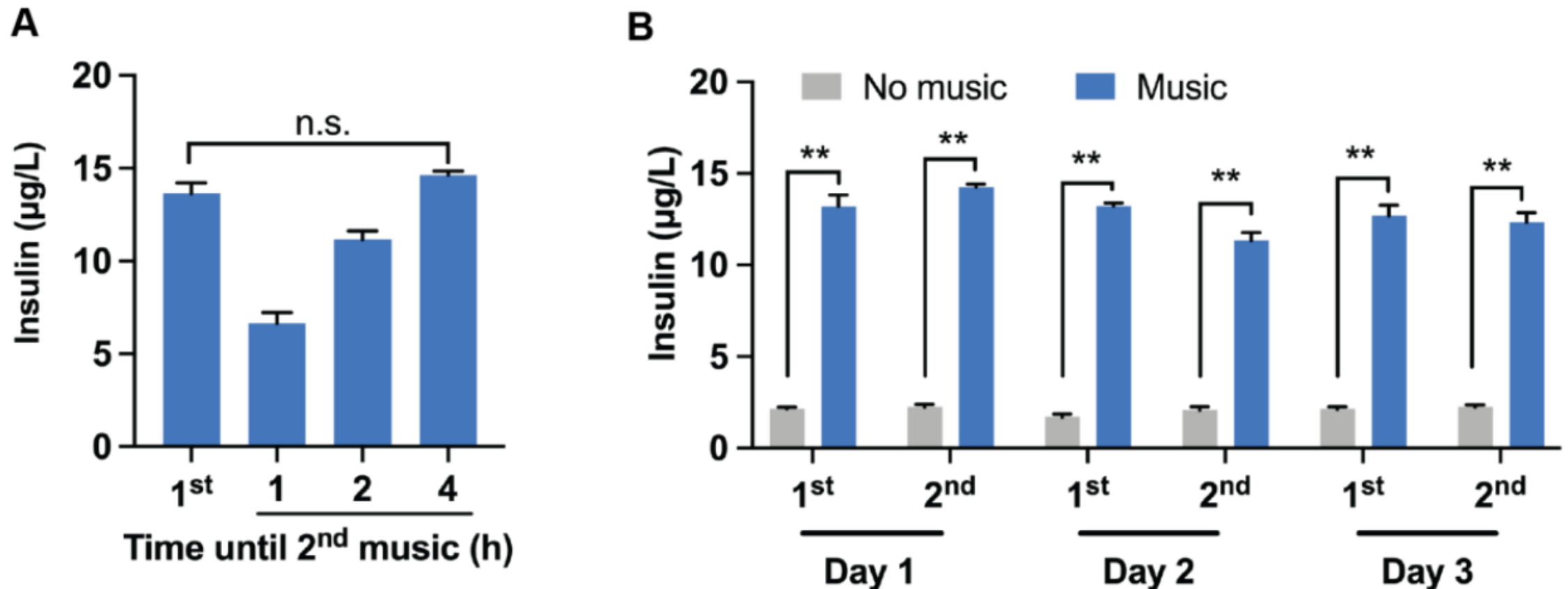
H Speech



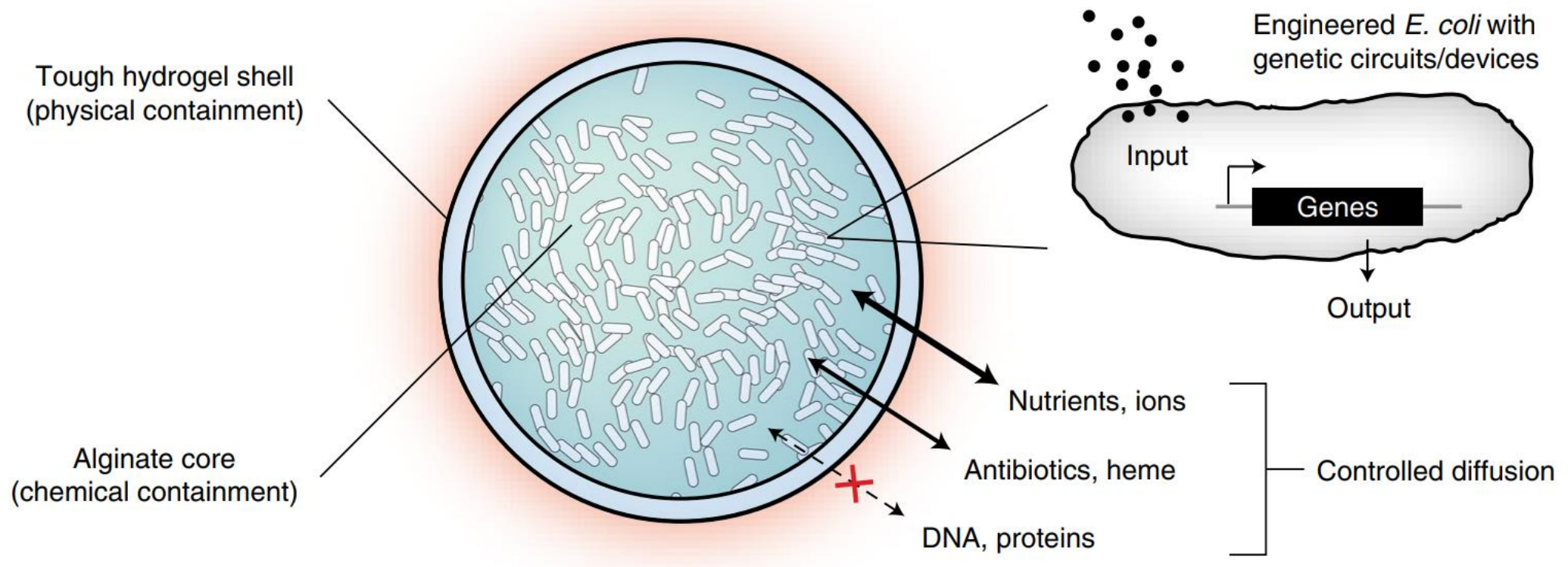
The dynamics of music-triggered insulin release by Queen's song, *We Will Rock You*



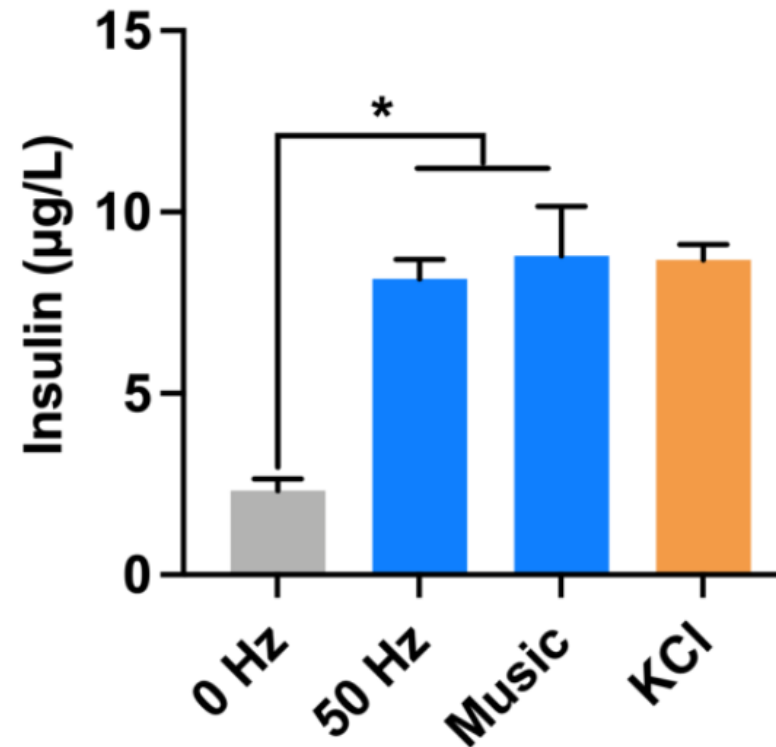
The cells reached a full insulin refill within 4 h consistently over several days



Coherent hydrogel microcontainers

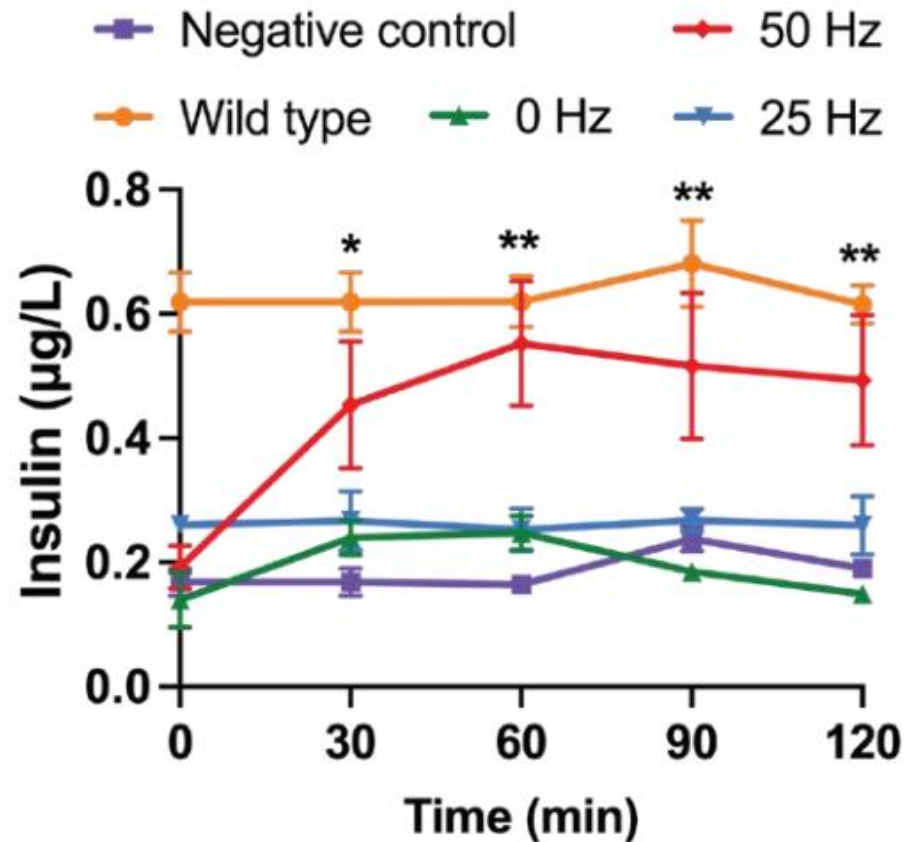


We confirmed music-sensitive insulin release by the microencapsulated cells

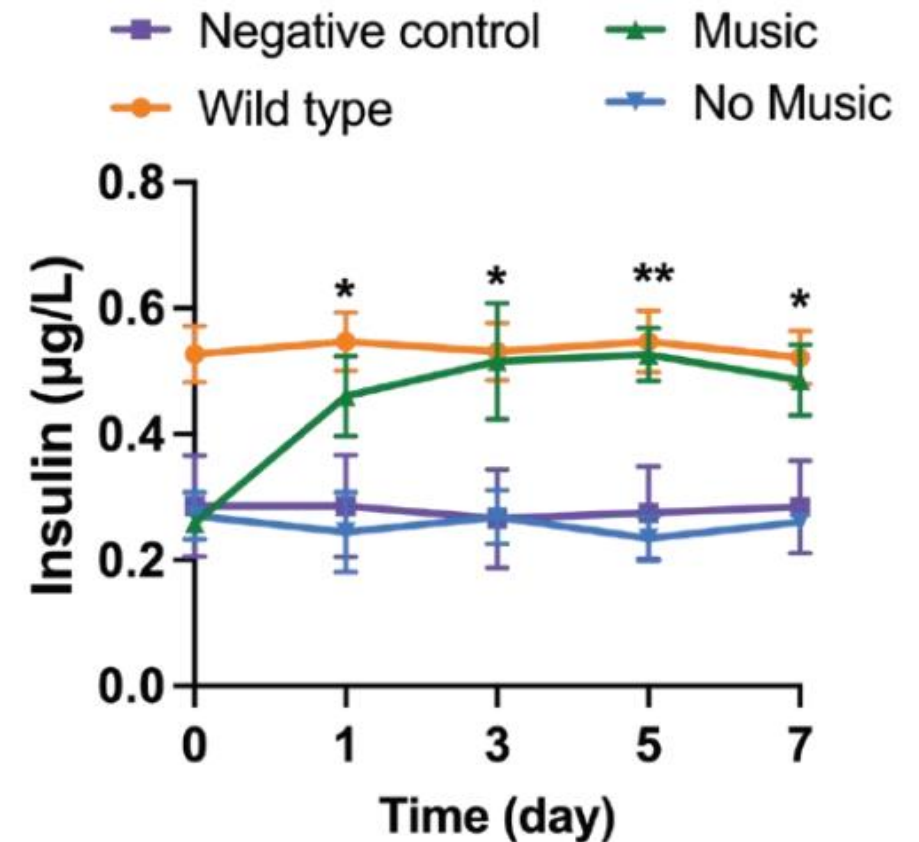


In vivo characterization

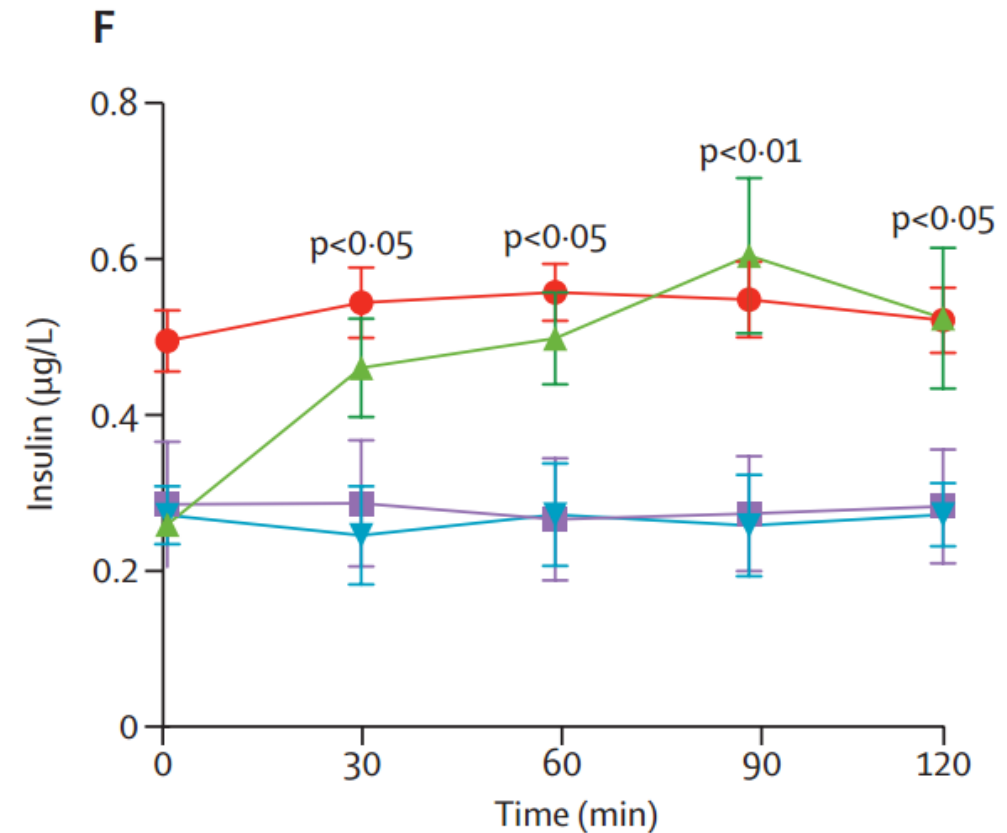
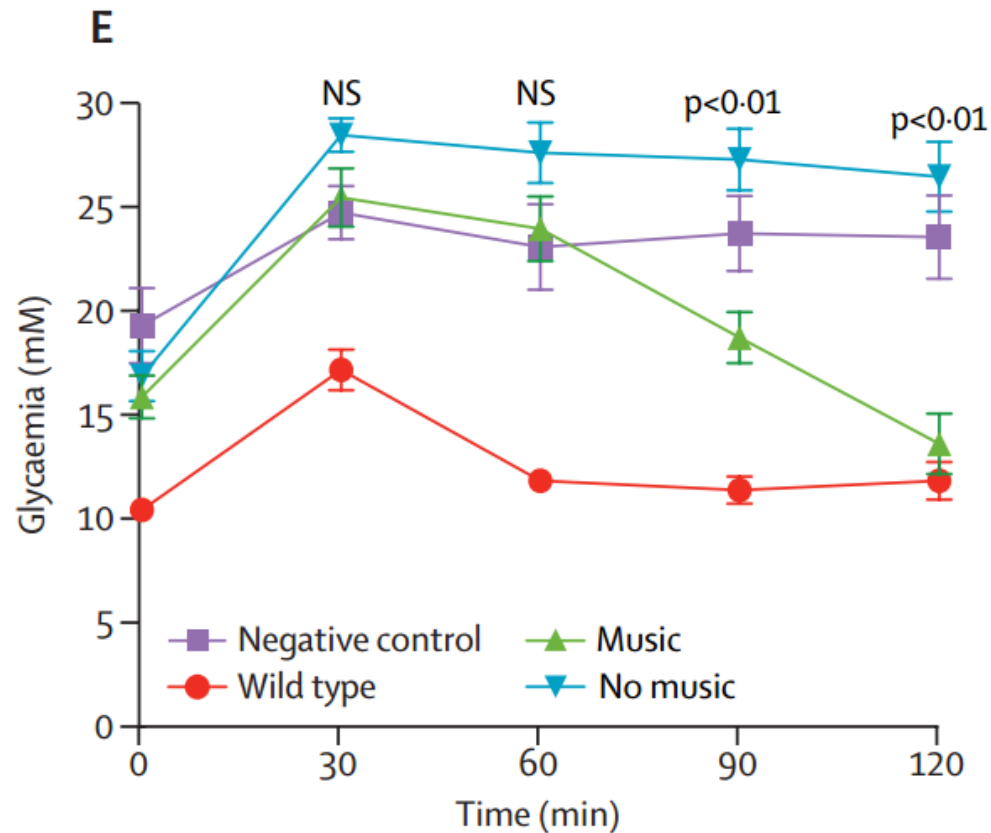
B



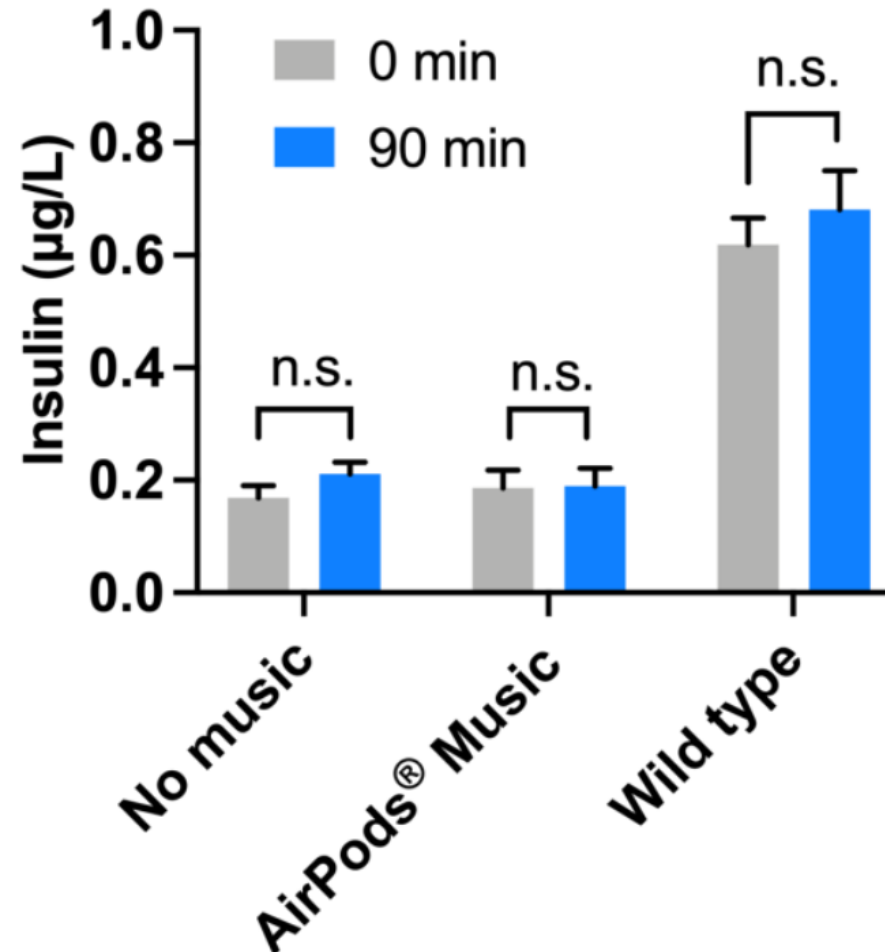
C



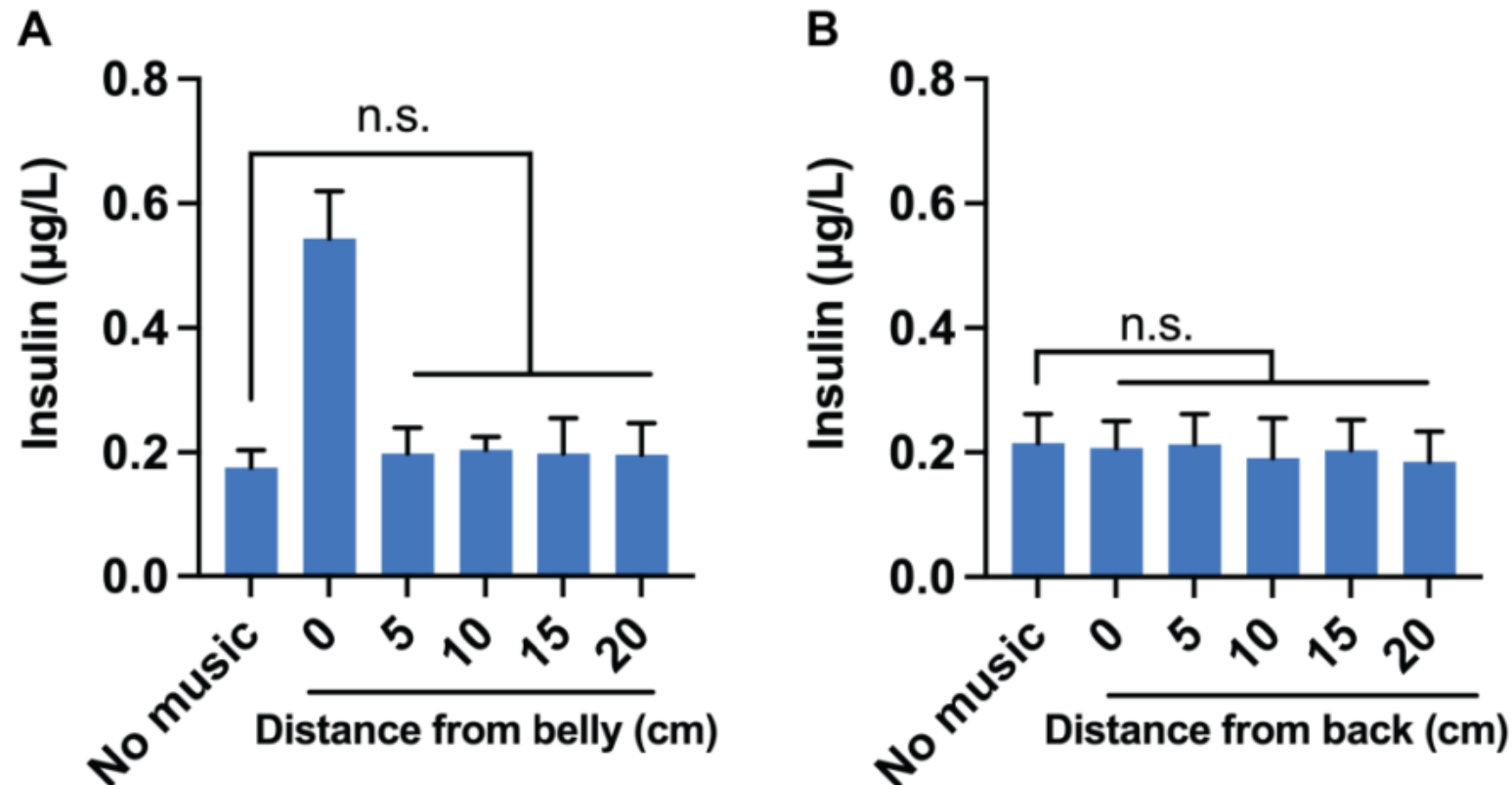
Attenuation of postprandial glycaemic excursions



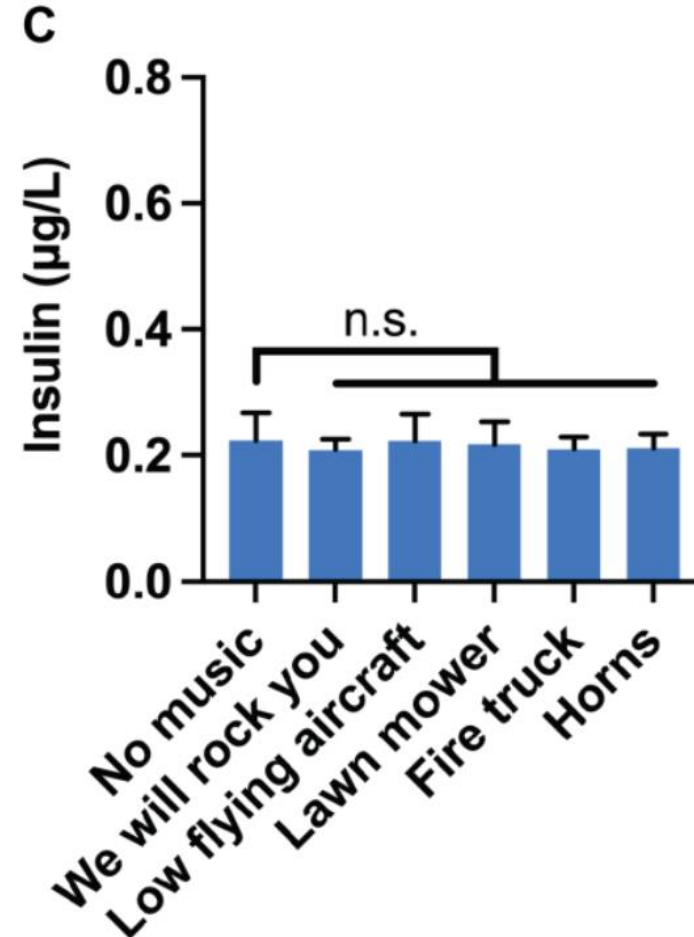
Commercial headphones or ear plugs did not trigger MUSIC_{INS}



MUSIC_{INS} cells are triggered only if the sound waves **directly impinge on the skin** just above the implantation site for at least 15 min



Various loud environmental noises did not result in undesired insulin secretion





1. MUSIC's vesicular secretion is much faster, and also enables a discontinuous peak delivery of protein therapeutics.
2. With only 4 h required for a full refill, MUSIC can provide several therapeutic doses a day.
3. MUSIC-transgenic cells can be stimulated by portable battery-powered commercial loudspeakers, with their bellies facing the speaker.

4. Its stimulation suffers from distance limitation.
5. How long can the cells live *in vivo*?
6. Safety concerns.

1.1E7 is a hybrid cell line formed by the electrofusion of a primary culture of human pancreatic islets with PANC-1, a human pancreatic ductal carcinoma cell line (ECACC catalogue number 87092802). 1.1E7 has been shown to be tumourigenic when transplanted into a SCID mouse



References

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