Researchers are developing a gene switch that triggers insulin release in designer cells by playing certain music

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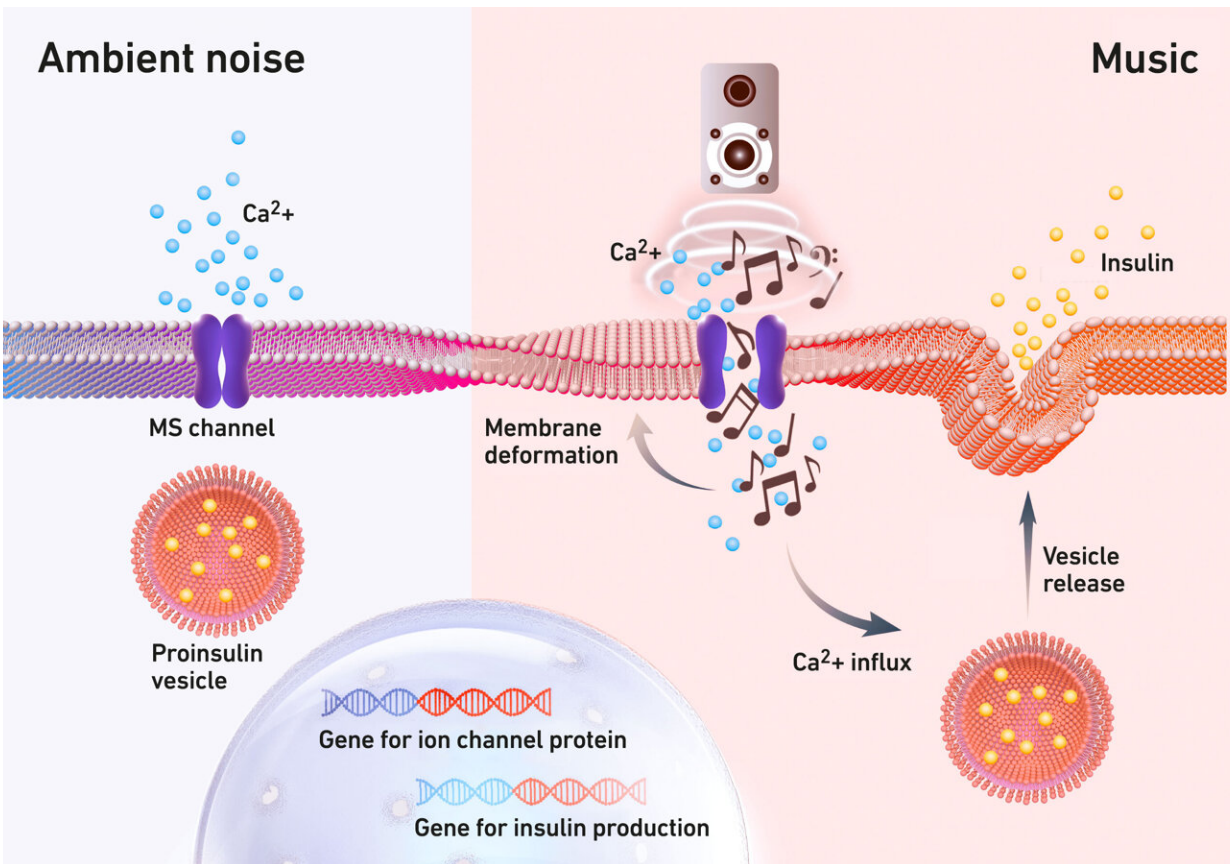

Ambient noise does not trigger insulin secretion (left). Direct exposure of the cells to certain rock songs, on the other hand, triggers insulin release within minutes (right). Credit: ETH Zurich

Diabetes is a condition in which the body produces too little or no insulin. Diabetics thus depend on an external supply of this hormone via injection or pump.

Researchers led by Martin Fussenegger from the Department of Biosystems Science and Engineering at ETH Zurich in Basel want to make the lives of these people easier and are looking for solutions to produce and administer insulin directly in the body. Their work has been published in *The Lancet Diabetes & Endocrinology*.

One such solution the scientists are pursuing is enclosing insulin-producing designer cells in capsules that can be implanted in the body. To be able to control from the outside when and how much insulin the cells release into the blood, researchers have studied and applied different triggers in recent years: light, temperature and electric fields.

Fussenegger and his colleagues have now developed another, novel stimulation method: they use music to trigger the cells to release insulin within minutes. This works especially well with "We Will Rock You," a global hit by British rock band, Queen.

Equipping cells to receive sound waves

To make the insulin-producing cells receptive to sound waves, the researchers used a protein from the bacterium E. coli. Such proteins respond to mechanical stimuli and are common in animals and bacteria. The protein is located in the membrane of the bacterium and regulates the influx of calcium ions into the cell interior.

The researchers have incorporated the blueprint of this bacterial ion channel into human insulin-producing cells. This lets these cells create the ion channel themselves and embed it in their membrane.

As the scientists have been able to show, the channel in these cells opens in response to sound, allowing positively charged calcium ions to flow into the cell. This leads to a charge reversal in the cell membrane, which in turn causes the tiny insulin-filled vesicles inside the cell to fuse with the cell membrane and release the insulin to the outside.

Booming bass boosts insulin secretion

In cell cultures, the researchers first determined which frequencies and volume levels activated the ion channels most strongly. They found that volume levels around 60 decibels (dB) and bass frequencies of 50 hertz were the most effective in triggering the ion channels. To trigger maximum insulin release, the sound or the music had to continue for a minimum of three seconds and pause for a maximum of five seconds. If the intervals were too far apart, substantially less insulin was released.

Finally, the researchers looked into which music genres caused the strongest insulin response at a volume of 85 dB. Rock music with booming bass like the song "We Will Rock You," from Queen, came out on top, followed by the soundtrack to the action movie "The Avengers." The insulin response to classical music and guitar music was rather weak by comparison.

"We Will Rock You" triggered roughly 70% of the insulin response within five minutes, and all of it within 15 minutes. This is comparable to the natural glucose-induced insulin response of healthy individuals, Fussenegger says.

Sound source must be directly above the implant

To test the system as a whole, the researchers implanted the insulin-producing cells into mice and placed the animals so that their bellies were directly on the loudspeaker. This was the only way the researchers could observe an insulin response. If, however, the animals were able to move freely in a "mouse disco," the music failed to trigger insulin release.

"Our designer cells release insulin only when the sound source with the right sound is played directly on the skin above the implant," Fussenegger explains. The release of the hormone was not triggered by ambient noise such as aircraft noise, lawnmowers, fire brigade sirens or conversations.

No triggering through ambient noise

As far as he can tell from tests on cell cultures and mice, Fussenegger sees little risk that the implanted cells in humans would release insulin constantly and at the slightest noise.

Another safety buffer is that insulin depots need four hours to fully replenish after they have been depleted. So even if the cells were exposed to sound at hourly intervals, they would not be able to release a full load of insulin each time and thereby cause life-threatening hypoglycemia.

"It could, however, cover the typical needs of a diabetes patient who eats three meals a day," Fussenegger says. He explains that insulin remains in the vesicles for a long time, even if a person doesn't eat for more than four hours. "There's no depletion or unintentional discharge taking place."

But clinical application is a long way off. The researchers have merely provided a proof of concept, showing that genetic networks can be controlled by mechanical stimuli such as sound waves.

Whether this principle will ever be put to practical use depends on whether a pharmaceutical company is interested in doing so. It could, after all, be applied broadly: the system works not only with insulin, but with any protein that lends itself to therapeutic use.

More information: Haijie Zhao et al, Tuning of cellular insulin release by music for real-time diabetes control, *The Lancet Diabetes & Endocrinology* (2023). DOI: 10.1016/S2213-8587(23)00153-5

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