BODY & BRAIN

A newborn's pain registers in the brain

Monitor picks up spikes in nerve cell activity after a jab or a stick

BY LAURA SANDERS

When a newborn is in pain, the brain shows an uptick in activity that scalp electrodes can detect, researchers say. Such activity could one day provide an objective measurement of pain.

An electrode on top of a newborn's scalp, near the soft spot, can measure when the baby feels pain. The method, described in the May 3 *Science Translational Medicine*, isn't foolproof, but it brings scientists closer to being able to tell when infants are in distress.

Pain assessment in babies is both difficult and extremely important for the same reason: Babies don't talk. That makes it hard to tell when they are in pain, and it also means that their pain can be more easily overlooked, says Carlo Bellieni, a pediatric pain researcher at the University Hospital Siena in Italy.

Doctors rely on a combination of clues such as crying, wiggling and facial grimacing to guess whether a baby is hurting. But these clues can mislead. "Similar behaviors occur when infants are not in pain, for example if they are hungry or want a cuddle," says study coauthor Rebeccah Slater of the University of Oxford. By relying on brain activity, the new method offers a more objective measurement.

Slater and colleagues measured brain activity in 18 newborns between 2 and 5 days old. Electroencephalography, or EEG, recordings from electrodes on the scalp picked up collective nerve cell activity as babies received a heel lance to draw blood or a low-intensity bop on the foot, a touch that's a bit like being gently poked with a blunt pencil. One electrode in particular, called the Cz electrode and perched on the top of the head, detected a telltale neural spike between 400 and 700 milliseconds after the painful event. This response wasn't observed when these same babies received a sham heel lance or an innocuous touch on the heel.

The Cz electrode detected similar brain responses to painful procedures in tests of 14 other newborns. Loud sounds, flashing lights and nonpainful touches didn't elicit the same response in those newborns. What's more, this brain signature changed when pain-relieving gel was used in another group of 12 babies who were on average 25 days old. After treatment with the topical anesthetic tetracaine, babies' brain responses to foot thumps were smaller than when the taps were delivered to unmedicated feet.

On average, babies born prematurely between 34 and 36 weeks gestation showed similar neural responses to pain. It's unclear whether this presumed pain signature would be present in babies born earlier or in older infants, Slater says.

In its current form, the method isn't reliable enough to be a definitive readout of pain in individual babies because not all babies' brains responded to pain similarly. Ten of 28 babies who had heel lances didn't show this neural signature.

And the brain signature didn't always track with other pain indicators. Of the 17 babies who indicated pain by changing facial expressions during a presumably painful event, 13 also showed the brain activity signature and four did not. Of the 11 babies who did not change expressions, five showed the brain signature and six did not. Slater says that a combination approach that relies on multiple indicators of pain might be useful.

Even if improved, this method might not be clinically useful, Bellieni says. A method that measures quick, severe pain can't be used to change a painful situation in real time. "When you get the results, the procedure is already over," he says.

BODY & BRAIN

New 'rules' for finding antibiotics

Tests give clues to fighting gram-negative bacteria

BY AIMEE CUNNINGHAM

Like entry to an exclusive nightclub, getting inside a gram-negative bacterial cell is no easy feat for chemical compounds. But now a secret handshake has been revealed: A new study lays out several rules to successfully cross the cells' fortified exteriors, which could lead to the development of sorely needed antibiotics.

"It's a breakthrough," says microbiologist Kim Lewis of Northeastern University in Boston, who was not involved with the work. The traditional way to learn how compounds get across the bacterial barrier is to study the barrier, he says. The researchers "decided to attack the problem from the other end: What are the properties of the molecules that may allow them to penetrate across the barrier?" The work describing these properties is reported online May 10 in *Nature*.

E. coli and other gram-negative bacteria — so described because of how they look when exposed to a violet dye called a gram stain — have two cellular membranes. The outer membrane is impermeable to most antibiotics, says chemical biologist Paul Hergenrother of the University of Illinois at Urbana-Champaign. "Even if a drug might be really good at killing that gram-negative pathogen, it may not be able to get in the bacteria."

Many antibiotics that have been effective against gram-negative bacteria are becoming unreliable, as the bugs have developed resistance. To encourage drug development, in February the World Health Organization released a list of pathogens that are resistant to multiple drugs. All of the bacteria in the "critical" priority group are gram-negative.

Gram-negative cells' outer membrane is dotted with proteins called porins. These channel structures allow the cells to take up nutrients. Antibiotics that get inside gram-negative bacteria typically pass through porins, Hergenrother says.

To uncover the dos and don'ts of porin passage, Hergenrother's group synthesized 100 compounds that share characteristics with antimicrobials found in nature, such as those from plants. The researchers took each compound, incubated it with *E. coli* bacteria in a tube for 10 minutes and then measured how much got inside the cells.

One feature stood out among the dozen compounds that significantly accumulated inside the bacterial cells: They all contained an amine group, a chemical group that contains the element nitrogen.

Next, the team collected a larger set of compounds that have amine groups and again measured whether the compounds accumulated inside *E. coli* cells. The researchers used a computer program to predict what other attributes would be necessary to get through porins. This analysis revealed that a compound should be rigid (rather than flexible) and flat (as opposed to spherical). It's much easier to put a ruler through a narrow opening than a basketball, notes Hergenrother.

To test the new rules, the researchers turned to an antimicrobial known as deoxynybomycin. This compound is effective only against gram-positive bacteria, which have just one cellular membrane. Deoxynybomycin is flat and rigid, so it already has "the right geometrical parameters," Hergenrother says. That makes it a good compound "to try to add an amine to, in a place that doesn't disrupt how it interacts with the biological target."

The team synthesized a derivative of deoxynybomycin with an amine group and tested the compound against a number of gram-negative pathogens that are resistant to many antibiotics. The altered deoxynybomycin successfully killed all but one of the types of pathogens tested.

It's possible other antibiotics that specifically target gram-positive bacteria could be converted into drugs that kill gram-negative bugs too by following the new rules, Hergenrother says. And keeping these guidelines in mind when assembling compound collections could make screening for drug candidates more successful.

The research could also "revive the failed effort to rationally design antibiotics," Lewis says. Knowing the rules, it may be possible to build a compound that both hits its bacterial target and has the features needed to penetrate the target's barrier. ■

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ATOM & COSMOS

Comet's oxygen may be homegrown

Newfound chemical reaction could produce the gas on 67P

BY ASHLEY YEAGER

Molecular oxygen detected around comet 67P may not be primordial. Instead the gas may be created by interactions of water, the solar wind and sand on 67P's surface, researchers suggest.

NAVCAM/ROSETTA/ESA (CC BY-SA IGO 3.0)

Oxygen on comets might not date all the way back to the birth of the solar system.

Instead, interactions between water, particles streaming from the sun and grains of sand or rust on the comet's surface could generate the gas. Those interactions could explain the surprising abundance of molecular oxygen detected in the fuzzy envelope of gas around comet 67P/Churyumov-Gerasimenko in 2015 (*SN: 11/28/15, p. 6*), researchers report May 8 in *Nature Communications*. Such reactions might also reveal how O_2 forms in other regions of space.

"Molecular oxygen is very hard to find out there in the universe," says Caltech chemical engineer Konstantinos Giapis. When the Rosetta spacecraft detected oxygen around 67P, astronomers argued it was primordial, trapped in water ice as the comet formed about 4.6 billion years ago. Giapis and Caltech colleague Yunxi Yao wanted to see if an alternative way to create O_2 existed. Drawing on their work with fast-moving charged particles and materials such as silicon, they performed experiments that showed that charged water particles could slam into rust or sand grains and generate O_2.

Something similar could happen on comet 67P, Giapis and Yao suggest. As the sun evaporates water from the comet's surface, ultraviolet light could strip an electron from the water, giving it a positive charge. Then, fast-moving particles in the solar wind could shoot the ionized water back toward the comet's surface, where it could collide with rust or sand particles. Atoms of oxygen from the water could pair with atoms of oxygen from the rust or sand, creating O_2.

The idea is plausible, says astrophysicist Paul Goldsmith of NASA's Jet Propulsion Laboratory in Pasadena, Calif. He helped discover O_2 in the Orion nebula and says the reaction might happen in places where young stars are forming and in other regions of space.

Rosetta mission scientist Kathrin Altwegg of the University of Bern in Switzerland is skeptical the new work explains comet 67P's O_2. As the comet gets closer to the sun, a protective bubble develops around 67P, Rosetta data show; that bubble would prevent solar wind or other ionized particles from reaching the comet's surface, Altwegg says. The ratio of oxygen to un-ionized water also stays constant over time. It should be variable if this chemical reaction were generating oxygen, she says.

Goldsmith suggests researchers keep an open mind and design missions to test whether this newly detected reaction does, in fact, generate oxygen in space. ■