BIO NEWS

October, 2017

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目次

2017 年 9 月のニュース

＝研究編（詳細については各番号をクリックして下さい)＝

2017 年 9 月のニュース

＝企業関連ニュース他＝

・日経の報道とは異なり、AstraZeneca から買収提案はなかったと第一三共 (9/1)
・FDA、カリフォルニア州とフロリダ州の幹細胞クリニックに警告 (9/4)
・Sanofi、米国陸軍由来のジカワクチン開発をやめる (9/4)
・次の主力薬の開発を成功させた Vasant Narasimhan 氏を Novartis が新 CEO に任命 (9/4)
・アルツハイマー病 血液で診断 -京都府立医大 (9/5)
・腫瘍を完全に摘出できたかを直ぐに確認しうるライトシート顕微鏡技術ができた (9/5)
・遺伝の「優性」「劣性」使うのやめます 学会が用語改訂 (9/6)
・ASCO 報告が注目された 2 社・Deciphera と Nucana が 1 億ドル規模の IPO 調達を計画 (9/6)
・Merck KGaA、店頭販売医療製品事業の売り出しを開始 (9/6)
・Merck、ドイツの抗腫瘍免疫誘導薬開発会社 Rigontec を買う (9/7)
・iPS 創薬、京大が初の治験承認 筋肉に骨できる難病で (9/7)
・ヒアリ「夏はポテチ派、冬は甘党」 専門家が好みを紹介 (9/7)
・貧困地域向けの非営利ワクチン事業にゲイツ基金が 1 億 2,000 万ドルを提供 (9/8)
・Lilly、世界で従業員 3,500 人を削減～2 つの研究開発拠点を閉鎖 (9/8)
・中国の医療技術に 2 億 5,000 万ドルを投資するファンドを Fidelity が発足 (9/9)
・EpiPen 回収の直前に米国 FDA 査察があって違反が見つかっていた～警告通知公開 (9/9)
・乳がん手術不要患者を判別 遺伝子特定、4 年後実用化へ -国立がん研究センター東病院（千葉県柏市）(9/10)
・妊娠でお腹の皮膚が広がるのはなぜ？ マウス実験で解明 -京大 (9/11)
・座り続ける生活で死亡リスク増、「３０分毎に運動を」-米研究 (9/12)
・Lundbeck の CEO・Kare Schultz 氏が Teva の CEO になる (9/12)
・J&J、C 型肝炎薬開発中止～今後は B 型肝炎に専念 (9/12)
・肥満に影響する遺伝マーカーを解明（112 の新たな遺伝的特徴を発見）-理研 (9/12)
・基礎研究を長い目で支援 ノーベル賞大隅氏が財団設立 (9/13)
・遺伝子治療開発会社 Rocket Pharmaceuticals が苦境の Inotek を買収 (9/14)

・AstraZeneca の研究開発のリーダーSanjay Jariwala 氏が Biogen に転職（9/14）
・ヒアリ毒液由来のソレノプシン化合物がセラミド様の働きで乾癬病態を解消（9/14）
・遺伝子変異疾患の治療を開発している BridgeBio Pharma が 1 億 3,500 万ドル調達（9/14）
・抑えられぬ食欲、メカニズム解明　肥満治療への応用期待　-基礎生物学研究所（愛知）（9/15）
・サンディエゴの耳治療薬の Otonomy、非営業人員の 1/3 削減～今年はもう臨床試験開始の予定なし（9/15）
・AstraZeneca、麻酔薬一揃えの権利を Aspen Group に売却（9/17）
・Immunocore、感染症治療の開発にゲイツ基金が最大 4,000 万ドル投資（9/19）
・ハーバード大学の Greg Verdine 氏の次の新会社 LifeMine は真菌由来の薬を開発（9/19）
・Teva、女性健康製品の売却で 24 億 8,000 万ドルの借金を返済（9/19）
・東アジアのピロリ菌他地域より強力、胃がん多い要因 -東大 (9/20)
・米国の多くの保険会社は値が張る鎮痛剤の使用に制限をかけている（9/20）
・ノーベル化学賞候補に新型太陽電池を研究する宮坂力（つとむ）桐蔭横浜大学特任教授 -米の学術情報会社（9/20）
・J&J、インフルエンザなどの感染流行への治療を米国政府と協力して揃える（9/21）
・AI で臨床試験の進め方を改善する Datavant をテック業界重鎮 Travis May 氏が率いる（9/21）
・Pfizer、Remicade のバイオシミラーを不当に締め出しているとして J&J を告訴（9/21）
・武田医学賞、木下タロウ阪大教授と小川誠司京大教授に（9/22）
・大製薬会社で 30 年近い R&D 経験を有する John Houston 氏が Arvinas 社 CEO に昇進（9/22）
・上海拠点の Zai Lab 社が 1 億 5,000 万ドルを IPO 調達～Nasdaq に上場（9/22）
・新規抗生剤の開発が全く追いついていない/WHO 見解（9/22）
・インドの新生児や小児の死亡率が以前に比べて低下（9/25）
・Gilead、C 型肝炎薬 Sovaldi が中国で承認された（9/26）
・Pfizer からの 4 剤の臨床開発を手がける新会社 SpringWorks が発足（9/26）

・フィラデルフィアの Spark Therapeutics、仏の遺伝治療開発リーダーFederico Mingozzi 氏を最高科学責任者に任命 (9/26)
・＜疫学調査＞魚たくさん食べる人、うつ病リスク半減 -国立がんセンター＆慶大チーム (9/27)

目次に戻る

1．腸内細菌が遺伝子の保護効果を変える可能性 -マウス実験

2017 年 8 月 30 日

1 型糖尿病およびその他の自己免疫疾患を予防するガーディアン（保護）遺伝子は、腸内細菌を変化させることによってその膵臓遮断効果を発揮する。強力な保護遺伝子を持って生まれたマウスを用いての実験により、重要な発達期間中に抗生物質を服用させることによって膵臓に重度の炎症（1 型糖尿病の前駆物質）を発症し、腸内微生物叢を変化させることによって遺伝子保護が失われることが示された。
この知見を 8 月 21 日の米国科学アカデミー紀要で発表したハーバード大学医学部の科学者らは、この結果が、妊娠後期および初期幼児期の抗生物質使用を避けることの重要性を強調するものだ、と述べている。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170830155511.htm

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Protecting the guardians

Gut bacteria can alter the protective effects of a gene that wards off type 1 diabetes

Date:

August 30, 2017

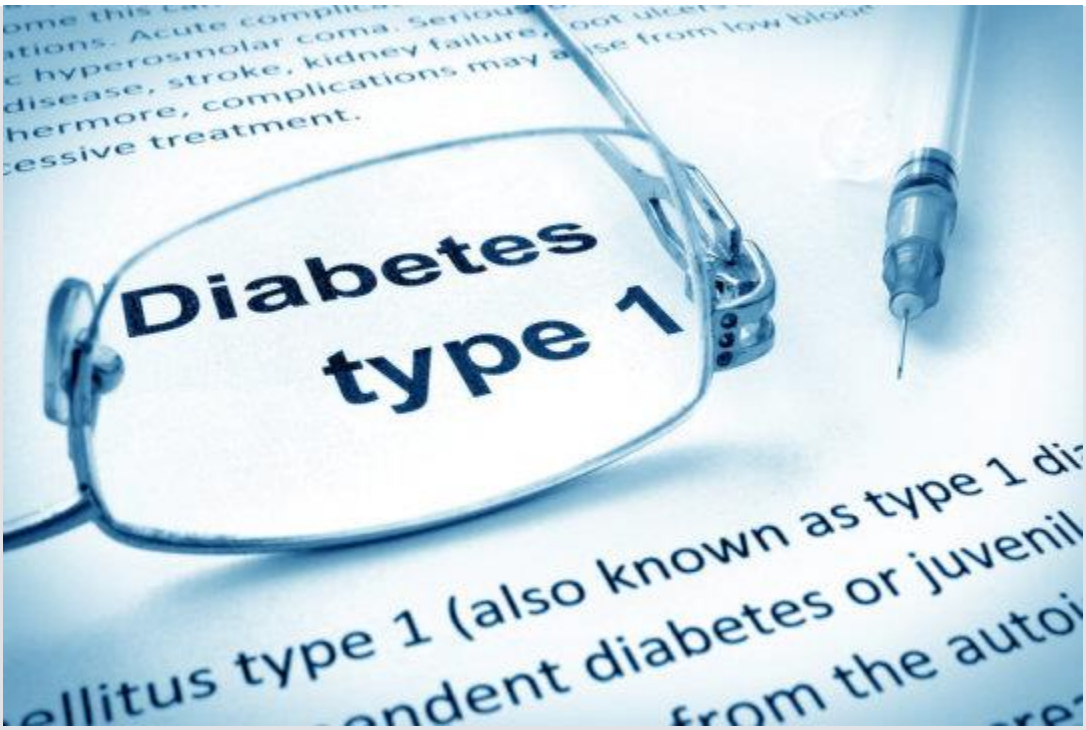
Source:

Harvard Medical School

Summary:

A guardian gene that protects against type 1 diabetes and other autoimmune diseases exerts its pancreas-shielding effects by altering the gut microbiota. Experiments in mice born with the protective gene show that exposure to antibiotics during critical windows of development fuels risk for type 1 diabetes and leads to loss of genetic protection by altering the gut microbiota. Scientists say the findings underscore the importance of avoiding antibiotic use during late pregnancy and early infancy.

FULL STORY



Diabetes concept (stock image). A new study found that despite harboring a powerful guardian gene, mice developed severe inflammation of the pancreas -- a precursor to type 1 diabetes -- after receiving antibiotics shortly after birth or if raised in a sterile environment.

Credit: © designer491 / Fotolia

Keeping the immune system in balance is no small feat. It must remain keenly alert to spot and disarm foreign invaders and smart enough to recognize the

body's own tissues and organs to spare them from a misdirected attack -- a mistken response known as autoimmunity.

Some of the workhorses that keep the immune system in check are tiny proteins on the surface of cells encoded by a set of guardian genes -- human leukocyte antigen (HLA) in humans and major histocompatibility complexes (MHC) in mice. Scientists have long known that certain common variants of the HLA/MHC genes protect against a range of autoimmune diseases, notably type 1 diabetes.

Yet how these genes and the tiny cell proteins they regulate yield their immune-modulating effects has remained shrouded in mystery. Now, a study in mice led by scientists at Harvard Medical School reveals that at least one of these genes has a protective influence that is powerfully shaped by the trillions of intestinal bacteria collectively known as the gut microbiota.

The team's experiments, published Aug. 21 in the *Proceedings of the National Academy of Sciences*, show that despite harboring the powerful guardian gene, mice developed severe inflammation of the pancreas -- a precursor to type 1 diabetes -- after receiving antibiotics shortly after birth or if raised in a sterile environment.

The new findings demonstrate that gut bacteria are potent catalysts of autoimmunity and pancreatic cell function and that perturbations in the gut microbiota can precipitate diabetes. The results also open up avenues for immune-modulating therapies targeted at maintaining the delicate bacterial balance of the gut microbiota.

"We believe that our results not only offer a clue into a longstanding mystery but also raise the possibility that substances or environmental influences that alter the intestinal balance can modulate the effects of a powerfully protective gene and shape disease risk," said Diane Mathis, who led the study together with Christophe Benoist, both professors in the Department of Microbiology and Immunobiology at Harvard Medical School.

The researchers caution that there are important physiological differences between mice and humans and emphasize that further studies are needed to elucidate precisely how gut bacteria affect gene activity and the risk for an autoimmune attack on the pancreas.

However, the scientists say their results highlight the role of the gut in proper immune function and point to the existence of a critical window in the proper development of the gut microbiome -- a time during which the intestines get populated with a variety of bacteria.

"Our findings need to be borne out in further experiments," Mathis said. "However, our results powerfully illustrate the notion that early antibiotic exposure can modulate disease risk and that avoiding or at least minimizing antibiotic treatment in infants and pregnant women during critical periods of development may be a good idea."

Type 1 diabetes, a disorder estimated to affect more than 1.2 million Americans, is marked by dysfunction of the insulin-producing cells of the pancreas. The condition leads to a dangerous buildup of sugar in the body that, over time, can take a serious toll on the heart, kidneys, eyes and brain. Unlike the far more common type 2 diabetes, which develops as a result of excessive weight, obesity and diet in mostly middle-aged and older adults, type 1 diabetes tends to strike younger adults and children.

In the study, researchers worked with mice bred to spontaneously develop diabetes, the classic animal model for studying the disease. However, this particular group was also bred to carry a protective gene variant shown in earlier studies to ward off type 1 diabetes despite the animals' heavy predisposition to the disease.

When treated with antibiotics in the first six weeks of life, mice went on to develop pancreatic inflammation, a precursor to type 1 diabetes, despite carrying the guardian gene. Treatment with antibiotics later in life -- between six and 10 weeks after birth -- did not lead to loss of protection against diabetes. The observation suggests a period during which the newborn gut is seeded by various germs, the researchers say. Interfering with that process by administering antibiotics appears to disrupt the balance of the gut microbiota, which in turn leads to loss of genetic protection, the researchers added.

Interestingly, mice whose protective gene was passed on by the father went on to develop diabetes. Mice that inherited a copy of the guardian gene from their mother, however, were resistant to diabetes. The

observation highlights the critical protective role of exposing a newborn to the mother's microbiota, which is passed on during birth.

Mice whose mothers had been given antibiotics in the 10 days before giving birth lost their genetic protection, the researchers found, and went on to develop pancreatic inflammation. Mice born with the protective gene but raised in sterile cages and deprived of bacterial exposure during early development never acquired gut microbial balance and disease protection. These animals developed severe pancreatic inflammation typically seen in diabetic mice. This observation, the researchers say, further underscores the importance of early environmental exposures to a variety of germs in the proper development of the immune system. The researchers note that the finding is also consistent with the so-called hygiene hypothesis, which posits that the declining number of childhood infections and lack of sufficient germ exposure during early childhood may fuel a person's lifetime risk for allergic and autoimmune diseases. That link, however, the researchers caution, has yet to be proven.

In a final set of experiments, the team performed fecal transplants in diabetes-prone mice without the protective gene using fecal matter obtained from mice that carried the guardian gene. Following fecal transplantation, the diabetes-prone mice exhibited dramatically reduced pancreatic cell inflammation and did not develop diabetes -- a finding that further affirms the role of gut bacteria as a powerful modulator of disease.

Co-investigators include Michael Silverman, Lindsay Kua, Alessandro Tanca, Mauro Pala, Antonio Palomba, Ceylan Tanes, Kyle Bittinger, and Sergio Uzzau.

The work was supported by The JPB Foundation, a gift from the Howalt family, by a Pediatric Infectious Disease Society Fellowship Award, the Juvenile Diabetes Research Foundation fellowship 10-2013-105, a Child Health Research Center K12 Award, the National Institutes of Health grant K08AI114970, and a National Science Foundation Fellowship DGE1144152.

Story Source:

Materials provided by **Harvard Medical School**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Michael Silverman, Lindsay Kua, Alessandro Tanca, Mauro Pala, Antonio Palomba, Ceylan Tanes, Kyle Bittinger, Sergio Uzzau, Christophe Benoist, Diane Mathis. **Protective major histocompatibility complex allele prevents type 1 diabetes by shaping the intestinal microbiota early in ontogeny**. *Proceedings of the National Academy of Sciences*, 2017; 201712280 DOI: 10.1073/pnas.1712280114

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Harvard Medical School. (2017, August 30). Protecting the guardians: Gut bacteria can alter the protective effects of a gene that wards off type 1 diabetes. *ScienceDaily*. Retrieved September 5, 2017 from www.sciencedaily.com/releases/2017/08/170830155511.htm
Harvard Medical School. "Protecting the guardians: Gut bacteria can alter the protective effects of a gene that wards off type 1 diabetes." ScienceDaily. www.sciencedaily.com/releases/2017/08/170830155511.htm (accessed September 5, 2017).

目次に戻る

2. ヒト細胞と「話す」腸内細菌が新しい治療に繋がる可能性 -マウス実験

2017 年 8 月 30 日

先週 *Nature* 誌に掲載されたロックフェラー大学とマウント・シナイ アイカーン医科大学（Icahn School of Medicine at Mt. Sinai）による新しい研究で、研究者らは腸内細菌とヒト細胞は多くの点で異なっているが、リガンドと呼ばれる分子に基づいて、基本的に同じ言語を話すことを発見した、としている。また、この新たに発見された共通性を用いて、ヒトの代謝を変えることによって特定の障害を治療する可能性のある分子を生産するための細菌を遺伝子操作する方法を開発した、としている。
この研究において、研究者らは、グルコースと食欲の調整に関与することで知られるヒト受容体 GPR119 に結合する特定のリガンド、N-アシルアミドを生産するように腸内細菌を操作した。彼らが作成した細菌のリガンドは、ヒトのリガンドと構造的にはほとんど同じであることが判明。マウス実験においては、改変された腸内細菌の導入で、マウスの血中グルコースレベルおよび他の代謝変化の減少も示している。

英文記事：
https://www.sciencedaily.com/releases/2017/08/170830141248.htm

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Gut bacteria that 'talk' to human cells may lead to new treatments

Date:

August 30, 2017

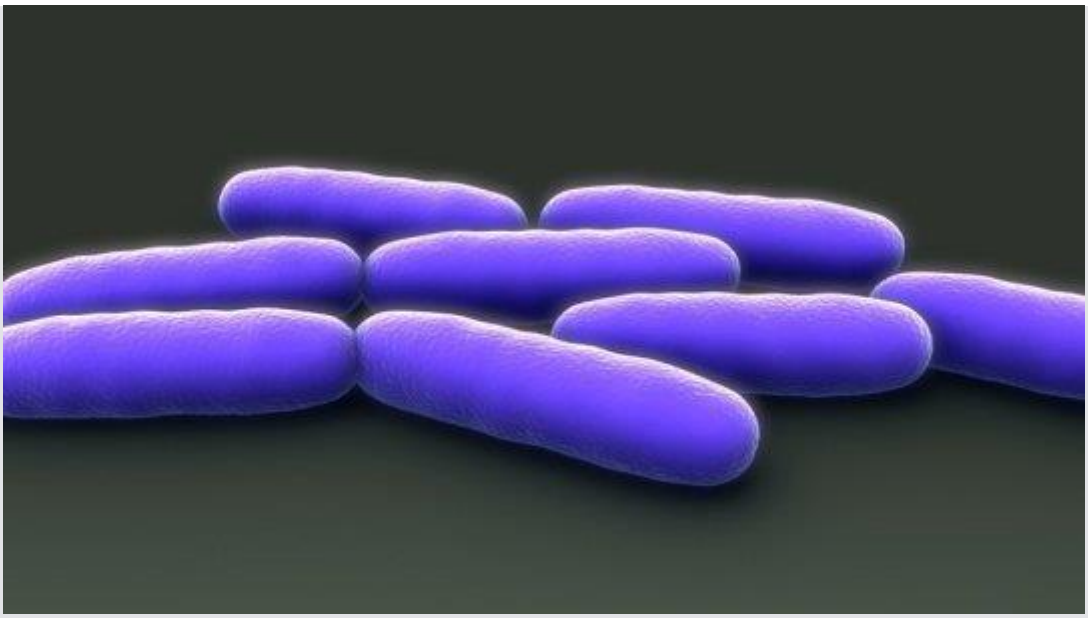
Source:

Rockefeller University

Summary:

Scientists developed a method to genetically engineer gut bacteria to produce molecules that have the potential to treat certain disorders by altering human metabolism.

FULL STORY



Bacteria (stock image).

Credit: © 7activestudio / Fotolia

We have a symbiotic relationship with the trillions of bacteria that live in our bodies -- they help us, we help them. It turns out that they even speak the same language. And new research from The Rockefeller University and the Icahn School of Medicine at Mt. Sinai suggests these newly discovered commonalities may open the door to "engineered" gut flora who can have therapeutically beneficial effects on disease.

"We call it mimicry," says Sean Brady, director of Rockefeller University's Laboratory of Genetically Encoded Small Molecules, where the research was conducted. The breakthrough is described in a paper published this week in the journal *Nature*.

In a double-barreled discovery, Brady and co-investigator Louis Cohen found that gut bacteria and human cells, though different in many ways, speak what is basically the same chemical language, based on molecules called ligands. Building on that, they developed a method to genetically engineer the bacteria to produce molecules that have the potential to treat certain disorders by altering human metabolism. In a test of their system on mice, the introduction of modified gut bacteria led to reduced blood glucose levels and other metabolic changes in the animals.

Molecular impersonation

The method involves the lock-and-key relationship of ligands, which bind to receptors on the membranes of human cells to produce specific biological effects. In this case, the bacteria-derived molecules are mimicking human ligands that bind to a class of receptors known as GPCRs, for G-protein-coupled receptors.

Many of the GPCRs are implicated in metabolic diseases, Brady says, and are the most common targets of drug therapy. And they're conveniently present in the gastrointestinal tract, where the gut bacteria are also found. "If you're going to talk to bacteria," says Brady, "you're going to talk to them right there." (Gut bacteria are part of the microbiome, the larger community of microbes that exist in and on the human body.)

In their work, Cohen and Brady engineered gut bacteria to produce specific ligands, N-acyl amides, that bind with a specific human receptor, GPR 119, that is known to be involved in the regulation of glucose and appetite, and has previously been a therapeutic target for the treatment of diabetes and obesity. The bacterial ligands they created turned out to be almost identical structurally to the human ligands, says Cohen, an assistant professor of gastroenterology in the Icahn School of Medicine at Mt. Sinai.

Manipulating the system

Among the advantages of working with bacteria, says Cohen, who spent five years in Brady's lab as part of Rockefeller's Clinical Scholars Program, is that their genes are easier to manipulate than human genes and much is already known about them. "All the genes for all the bacteria inside of us have been sequenced at some point," he says.

In past projects, researchers in Brady's lab have mined microbes from soil in search of naturally occurring therapeutic agents. In this instance, Cohen started with human stool samples in his hunt for gut bacteria with DNA he could engineer. When he found them he cloned them and packaged them inside *E. coli* bacteria, which is easy to grow. He could then see what molecules the engineered *E. coli* strains were making.

Although they are the product of non-human microorganisms, Brady says it's a mistake to think of the bacterial ligands they create in the lab as foreign. "The biggest change in thought in this field over the last 20 years is that our relationship with these bacteria isn't antagonistic," he says. "They are a part of our physiology. What we're doing is tapping into the native system and manipulating it to our advantage."

"This is a first step in what we hope is a larger-scale, functional interrogation of what the molecules derived from microbes can do," Brady says. His plan is to systematically expand and define the chemistry that is being used by the bacteria in our guts to interact with us. Our bellies, it turns out, are full of promise.

Story Source:

Materials provided by **Rockefeller University**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Louis J. Cohen, Daria Esterhazy, Seong-Hwan Kim, Christophe Lemetre, Rhiannon R. Aguilar, Emma A. Gordon, Amanda J. Pickard, Justin R. Cross, Ana B. Emiliano, Sun M. Han, John Chu, Xavier Vila-Farres, Jeremy Kaplitt, Aneta Rogoz, Paula Y. Calle, Craig Hunter, J. Kipchirchir Bitok, Sean F. Brady.

Commensal bacteria make GPCR ligands that mimic human signalling molecules. *Nature*, 2017; DOI: 10.1038/nature23874

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Rockefeller University. (2017, August 30). Gut bacteria that 'talk' to human cells may lead to new treatments. *ScienceDaily*. Retrieved September 5, 2017 from www.sciencedaily.com/releases/2017/08/170830141248.htm
Rockefeller University. "Gut bacteria that 'talk' to human cells may lead to new treatments." ScienceDaily. www.sciencedaily.com/releases/2017/08/170830141248.htm (accessed September 5, 2017).

目次に戻る

3. <ダウン症> に関する論文２本

1) 実験化合物でマウスのダウン症様学習障害が逆転（ジョンズホプキンズ大医学部）

2) ダウン症抑制の新化合物　出生前投与、マウスで効果（京大大学院医学研究科）

2017 年 9 月 4 日

ダウン症は最も多い染色体異常とされ、約 1000 人に 1 人確率で発生する。23 対ある染色体のうち 21 番が 1 本多い 3 本のため遺伝子が過剰に働いて神経細胞が誕生しにくくなり、知的障害につながることが多い。
今回、このダウン症に関する類似した論文が同時に発表されたので、比較しながら紹介する。

1) の研究は、ジョンズホプキンス大学医学部と NHI の共同研究で、*Science Translational Medicine* 誌の 9 月 4 日号に掲載された。
これによると、ダウン症様のマウスの出生日に一回のみ、ソニックヘッジホッグ経路アゴニストとして知られる小分子を与えた場合、学習と記憶を劇的に補った、としている。彼らは、ヒトの 21 番染色体上に見出される遺伝子の約半分が余分にコピーされるように遺伝子操作されたマウスを使用した。マウスはダウン症の人に似た多くの特徴を有し、使い慣れた空間をどのようにナビゲートするのか覚えておくことが難しく、水の迷路で泳いでいる間にマウスがどのようにプラットフォームを見つけたか追跡することによってこれを試験した、としている。
2) の研究は、京都大学大学院医学研究科の萩原正敏教授（化学生物学）らの研究チームらによるもので、近く米国科学アカデミー紀要に掲載される。
これによると、ダウン症の胎児を妊娠している母マウスに妊娠中期（妊娠 10～15 日目）に 1 日 1 回、神経細胞を作り出す神経幹細胞の増殖を促す化合物を投与したところ、胎児には大脳皮質が通常より薄くなるダウン症の特徴がでなかった、としている。彼らは、この化合物を 717 種類の候補から探し出し、「アルジャーノン」と命名した。チームによると、アルジャーノンが遺伝子の過剰な働きを抑制するた

め神経細胞が正常に増え、脳構造の異常や学習行動の低下を改善させたとみている。

英文記事：

1) https://www.sciencedaily.com/releases/2013/09/130904140946.htm

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Experimental compound reverses down syndrome–like learning deficits in mice

Date:

September 4, 2013

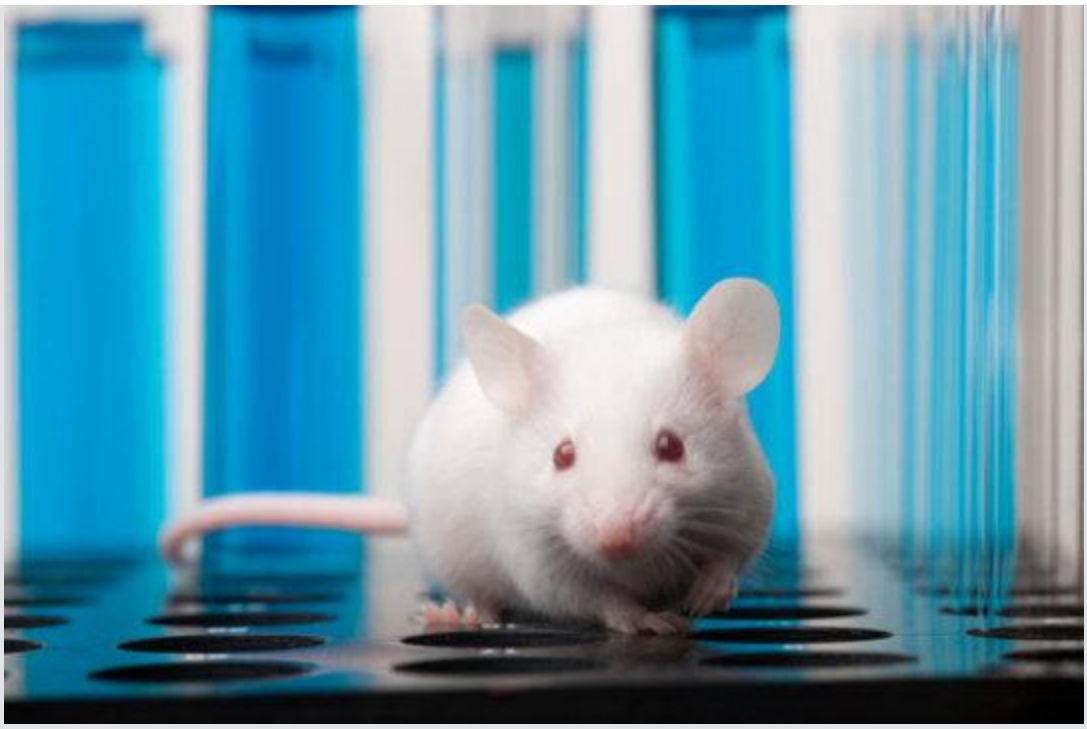
Source:

Johns Hopkins Medicine

Summary:

Researchers have identified a compound that dramatically bolsters learning and memory when given to mice with a Down syndrome-like condition on the day of birth. The single-dose treatment appears to enable the cerebellum of the rodents' brains to grow to a normal size.

FULL STORY



Laboratory mouse (stock image).

Credit: iStockphoto

Researchers at Johns Hopkins and the National Institutes of Health have identified a compound that dramatically bolsters learning and memory when given to mice with a Down syndrome-like condition on the day of birth. As they report in the Sept. 4 issue of *Science Translational Medicine*, the single-dose treatment appears to enable the cerebellum of the rodents' brains to grow to a normal size.

The scientists caution that use of the compound, a small molecule known as a sonic hedgehog pathway agonist, has not been proven safe to try in people with Down syndrome, but say their experiments hold promise for developing drugs like it.

"Most people with Down syndrome have a cerebellum that's about 60 percent of the normal size," says Roger Reeves, Ph.D., a professor in the McKusick-Nathans Institute of Genetic Medicine at the Johns Hopkins University School of Medicine. "We treated the Down syndrome-like mice with a compound we thought might normalize the cerebellum's growth, and it worked beautifully. What we didn't expect were the effects on learning and memory, which are generally controlled by the hippocampus, not the cerebellum."

Reeves has devoted his career to studying Down syndrome, a condition that occurs when people have three, rather than the usual two, copies of chromosome 21. As a result of this "trisomy," people with Down syndrome have extra copies of the more than 300 genes housed on that chromosome, which leads to intellectual disabilities, distinctive facial features and sometimes heart problems and other health effects. Since the condition involves so many genes, developing treatments for it is a formidable challenge, Reeves says.

For the current experiments, Reeves and his colleagues used mice that were genetically engineered to have extra copies of about half of the genes found on human chromosome 21. The mice have many characteristics similar to those of people with Down syndrome, including relatively small cerebellums and difficulty learning and remembering how to navigate through a familiar space. (In the case of the mice, this was tested by tracking how readily the animals located a platform while swimming in a so-called water maze.) Based on previous experiments on how Down syndrome affects brain development, the researchers tried supercharging a biochemical chain of events known as the sonic hedgehog pathway that triggers growth and development. They used a compound -- a sonic hedgehog pathway agonist -- that could do just that.

The compound was injected into the Down syndrome-like mice just once, on the day of birth, while their cerebellums were still developing. "We were able to completely normalize growth of the cerebellum through adulthood with that single injection," Reeves says.

But the research team went beyond measuring the cerebellums, looking for changes in behavior, too. "Making the animals, synthesizing the compound and guessing the right dose were so difficult and time-consuming that we wanted to get as much data out of the experiment as we could," Reeves says. The

team tested the treated mice against untreated Down syndrome-like mice and normal mice in a variety of ways, and found that the treated mice did just as well as the normal ones on the water maze test.

Reeves says further research is needed to learn why exactly the treatment works, because their examination of certain cells in the hippocampus known to be involved in learning and affected by Down syndrome appeared unchanged by the sonic hedgehog agonist treatment. One idea is that the treatment improved learning by strengthening communication between the cerebellum and the hippocampus, he says.

As for the compound's potential to become a human drug, the problem, Reeves says, is that altering an important biological chain of events like sonic hedgehog would likely have many unintended effects throughout the body, such as raising the risk of cancer by triggering inappropriate growth. But now that the team has seen the potential of this strategy, they will look for more targeted ways to safely harness the power of sonic hedgehog in the cerebellum. Even if his team succeeds in developing a clinically useful drug, however, Reeves cautions that it wouldn't constitute a "cure" for the learning and memory-related effects of Down syndrome. "Down syndrome is very complex, and nobody thinks there's going to be a silver bullet that normalizes cognition," he says. "Multiple approaches will be needed."

Other authors on the paper were Jung H. Shin of the National Institute on Alcohol Abuse and Alcoholism, and Ishita Das, Joo-Min Park, Soo Kyeong Jeon, Hernan Lorenzi, David J. Linden and Paul F. Worley, all of the Johns Hopkins University School of Medicine. The study was funded by the Down Syndrome Research and Treatment Foundation, Research Down Syndrome, the National Institute of Child Health and Human Development (grant number R01 HD38384), the intramural programs of the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Mental Health (grant number MH51106) and the National Institute of Neurological Disorders and Stroke (grant number R01 NS39156).

Story Source:

Materials

provided by **Johns Hopkins Medicine**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Ishita Das, Joo-Min Park, Jung H. Shin, Soo Kyeong Jeon, Hernan Lorenzi, David J. Linden, Paul F. Worley And Roger H. Reeves,†. **Hedgehog Agonist Therapy Corrects Structural and Cognitive Deficits in a Down Syndrome Mouse Model**. *Science Translational Medicine*, 2013 DOI: 10.1126/scitranslmed.3005983

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- MLA
- APA
- Chicago

Johns Hopkins Medicine. "Experimental compound reverses down syndrome-like learning deficits in mice." ScienceDaily. ScienceDaily, 4 September 2013. <www.sciencedaily.com/releases/2013/09/130904140946.htm>.

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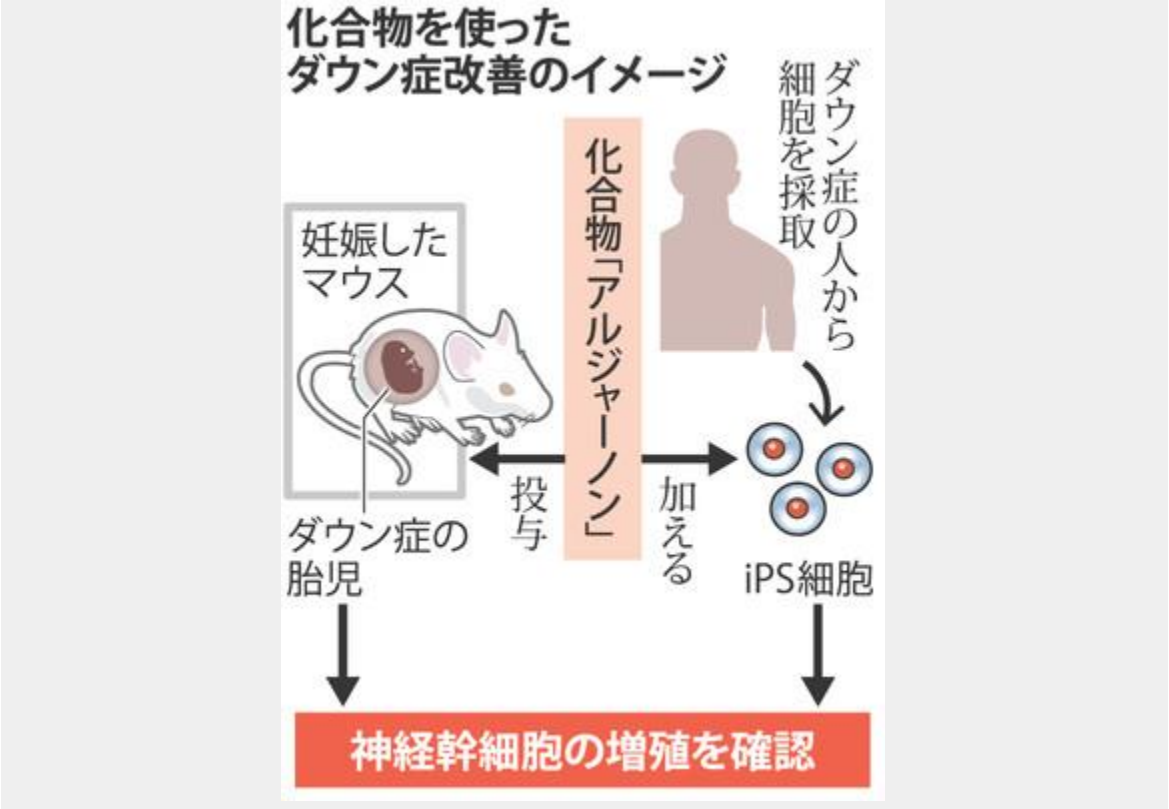
2)-1 https://headlines.yahoo.co.jp/hl?a=20170905-00000005-mai-sctch

＜ダウン症＞抑制の新化合物　出生前投与、マウスで効果

9/5(火) 4:00 配信

毎日新聞



化合物を使ったダウン症改善のイメージ

京都大大学院医学研究科の萩原正敏教授（化学生物学）らの研究チームは４日、ダウン症で知的障害を引き起こす原因の一つとされる遺伝子の働きを抑制する新たな化合物を発見したと発表した。ダウン症の胎児を妊娠している母マウスに投与したところ、胎児の脳構造の異常や学習行動が改善したことを確認した。ダウン症などの染色体異常を調べる出生前診断を受ける妊婦が増えているが、今回の研究は胎児期に治療できる可能性につながる成果という。論文は近く米科学アカデミー紀要に掲載される。

ダウン症は最も多い染色体異常とされ、約１０００人に１人の確率で発生する。

２３対ある染色体のうち２１番が１本多い３本のため遺伝子が過剰に働いて神経細胞が誕生しにくくなり、知的障害などにつながることが多い。

研究チームは、神経細胞を作り出す神経幹細胞の増殖を促す化合物を７１７種類の候補から探し出し、「アルジャーノン」と命名。ダウン症の赤ちゃんを妊娠した母マウスに、妊娠中期（妊娠１０～１５日目）に１日１回経口投与した。この結果、胎児には大脳皮質が通常より薄くなるダウン症の特徴が出なかった。迷路の正しい道を覚える出生後の学習行動実験では、通常のマウスと同程度に正しい場所を覚えていた。

チームによると、アルジャーノンが遺伝子の過剰な働きを抑制するため神経幹細胞が正常に増え、脳構造の異常や学習行動の低下を改善させたとみられる。ダウン症の人のｉＰＳ細胞（人工多能性幹細胞）から作った神経幹細胞も、正常に増えることを確認した。今後は神経細胞が関与している脳梗塞（こうそく）やアルツハイマー病、パーキンソン病も対象に研究を進める。萩原教授は「安全確認のハードルが高く、出生前治療に対する社会的な合意も必要だ」としている。【野口由紀】

◇治療活用、高いハードル

京都大チームが発見した新しい化合物は、胎内にいるダウン症のマウスだけでなく、ヒトのｉＰＳ細胞を使った実験でも効果が見られた。もし出生前のダウン症の治療薬が実現すれば影響は大きい。国内では出生前診断を受けて染色体異常が確定した人のうち、９０％以上が中絶に至っているとされる。治療の選択肢が示されれば、こうした状況に変化が起こる可能性がある。

研究チームは新化合物を「アルジャーノン」と名付けた。米国の作家ダニエル・キイスの小説「アルジャーノンに花束を」も意識したという。この小説に登場するアルジャーノンは、脳手術を受け高い知能を得るネズミの名前。ところがこの手術には、やがて知能を失う欠点があるというあらすじだ。

今回の新化合物にも課題はある。ダウン症は、複合的な疾患群だ。知的障害のほか、合併症として心臓病や聴力障害などを伴うこともある。アルジャーノンが神経幹細胞の増殖を促しても、先天性の心疾患が改善するわけではない。

創薬に向けたハードルも高い。臨床研究にまで至った場合、健康な妊娠した女性に薬を飲んでもらう必要があるからだ。

日本ダウン症協会は「障害は子どもの個性の一側面」として捉えている。ダウン症を「病気」として「治療」すべきなのか。新たな議論が必要となる局面も、いずれ来ることになるかもしれない。【池田知広】

◇画期的だが未知数

ダウン症の合併症治療に詳しい大薗恵一・大阪大教授（小児科学）の話
ダウン症の人には約８０の遺伝子が影響を与えている可能性があるとされ、今回の化合物がターゲットにしているのはそのうちの一つ。画期的な研究成果だが、人間でどこまでの効果が見込めるかは分からない。副作用の有無を確認する必要があり、創薬は一筋縄にはいかないだろう。

2)-2 http://京都新聞.jp/environment/article/20170905000001

ダウン症の脳、発達促す化合物　京大開発、マウスで確認

ダウン症と診断された胎児の脳の発達を促す可能性がある化合物を、京都大医学研究科の萩原正敏教授や小林亜希子助教らが開発した。妊娠中の母マウスに投与し、ダウン症モデルの子への効果を確認した。萩原教授は「人のダウン症へ使うには、安全面の課題を解決した上で社会的な合意が必要となる」と、慎重な見極めの必要性を強調した。米国科学アカデミー紀要に近く、発表する。

ヒトの場合、ダウン症は千人に1人の割合で生まれ、通常は2本の21番目の染色体が3本ある。知的障害や心臓病などを伴い、一部の遺伝子の過剰発現が原因とされる。

萩原教授らはダウン症で過剰に発現し、神経幹細胞の増殖を妨げるタンパク質「DYRK1A」に着目。ダウン症モデルのマウスの神経幹細胞に約700種類の化合物を作用させ、DYRK1Aの活性を抑制し、神経幹細胞の増殖を促すタイプを見つけた。このうち胎盤を通過して脳に到達しやすい化合物を、ダウン症の胎児を妊娠している母マウスに投与。胎児のマウスの大脳皮質は健常なマウスと同じ厚さとなった。生まれた子マウスは、迷路テストで健常なマウスと差のない学習能力を示した。

またダウン症患者から作ったヒトiPS細胞（人工多能性幹細胞）を使って化合物の作用を解析すると、ヒトの神経幹細胞を増殖させる機能が回復した。

萩原教授は「ダウン症だけでなく脳梗塞やパーキンソン病など、ほかの病気にも応用できるはず」としている。

■安全や倫理面、人への応用にはハードル

出生前に薬を投与し、ダウン症の脳の発達を促す可能性を示した研究。先天性疾患を研究する医師からは「実際に人へ投与するには効果や安全面で確認するべきハードルがたくさんある」という指摘が聞かれた。またダウン症の子のいる母親からは「豊かな感情などダウン症の人の魅力は大きい。知的な発達を一概に治療対象にするべきではない」と慎重意見も出た。

小児科医で先天性疾患の治療法を研究する神戸学院大の松尾雅文教授は、神経幹細胞の増殖を確認した成果を「成人の神経の病気などに広く応用できる可能性を示した」と評価。その上で「生まれた後の成長過程での副作用の有無など、安全性の確認にはかなり時間がかかる」と指摘した。また、マウスで確認した認知機能への効果をヒトに見いだせるかは、検証が必要と述べた。

次女（28）がダウン症で、生命倫理学を研究する近畿大理工学部の巽純子准教授は「出生前に子がダウン症と分かれば母親は悩む。ただダウン症の生の豊かさがもっと社会に理解されればとらえ方は変わるはず」と強調した。医療面での選択肢が増えることに理解を示しつつ、「ダウン症の全てを治療に結びつける必要はない」と話した。

また、今回の治療は出生前診断が前提となっている点を指摘。ダウン症と分かると中絶を選択するケースが多いことに触れ、「ゲノム（遺伝情報）の違いで差別されてはいけない。生まれてくる命を選別する是非はこれからも議論を続けていくべき」と注意を促した。

【2017 年 09 月 05 日 04 時 10 分】

目次に戻る

４．１つの強力な細胞があなたの習慣を変える -マウス実験

2017 年 9 月 6 日

デューク大学の神経科学者らは、脳内の深い場所で習慣の「マスターコントローラー」として働く単一のニューロンを特定した。
チームは習慣形成がこの影響力のある細胞の活性を高めること、また薬物でそれをシャットダウンすることによってマウスの砂糖を探す習性を簡単に破壊することを発見した。
9 月 5 日に *eLife* 誌に掲載されたこの研究は、ヒトにおける中毒あるいは脅迫行動に対する治療法に繋がる可能性がある、としている。

英文記事：
https://www.eurekalert.org/pub_releases/2017-09/du-opc090617.php

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PUBLIC RELEASE: 6-SEP-2017

One powerful cell makes or breaks your habits

Researchers pinpoint the neurons responsible for orchestrating habitual behavior

DUKE UNIVERSITY

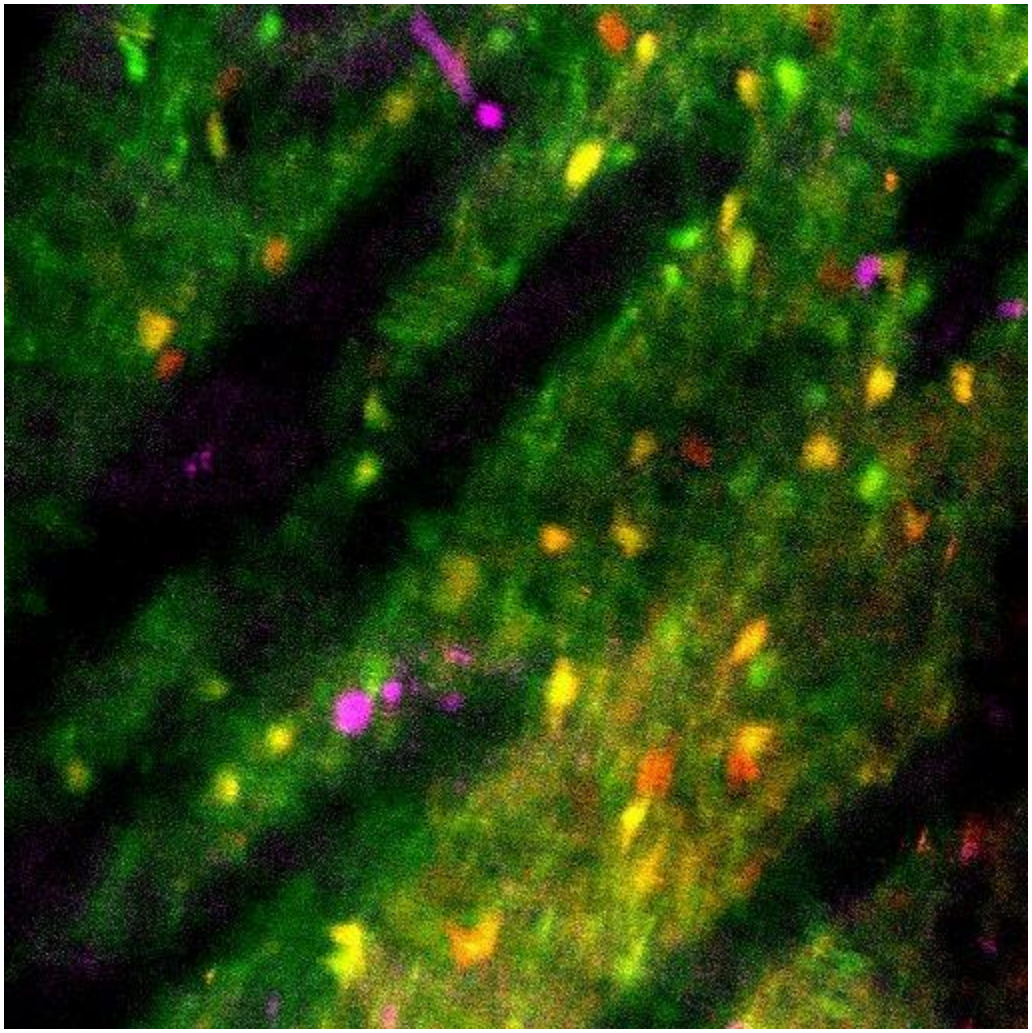

IMAGE: A highly magnified view of the striatum of a mouse brain reveals a relatively rare type of cell called the fast-spiking interneuron (purple), which is responsible for orchestrating the brain... view more

Credit: Justin O'Hare, Duke University

DURHAM, N.C. -- Some habits are helpful, such as automatically washing your hands before a meal or driving the same route to work every day. They accomplish an important task while freeing up valuable brain space.

But other habits -- like eating a cookie every day after work -- seem to stick around even when the outcomes aren't so good.

Duke University neuroscientists have pinpointed a single type of neuron deep within the brain that serves as a "master controller" of habits.

The team found that habit formation boosts the activity of this influential cell, and that shutting it down with a drug is enough to break habits in sugar-seeking mice. Though rare, this cell exerts its control through a web of connections to more populous cells that are known to drive habitual behavior.

"This cell is a relatively rare cell but one that is very heavily connected to the main neurons that relay the outgoing message for this brain region," said Nicole Calakos, an associate professor of neurology and neurobiology at the Duke University Medical Center. "We find that this cell is a master controller of habitual behavior, and it appears to do this by re-orchestrating the message sent by the outgoing neurons."

The findings, published Sept. 5 in *eLife*, may point towards new treatments for addiction or compulsive behavior in humans.

The team got their first glimpse into the neurological underpinnings of habit in a 2016 study that explored how habits can leave enduring marks on the brain. The research was a collaborative effort between Calakos' lab and Henry Yin, an associate professor in Duke's department of psychology and neuroscience.

The team trained otherwise healthy mice to receive a tasty treat every time they pressed a lever. Many mice developed a lever-pressing habit, continuing to press the lever even when it no longer dispensed treats, and despite having had an opportunity to eat all the treats they wanted beforehand.

The team then compared the brain activity of mice who had developed a lever-pressing habit with those who hadn't. They focused on an area deep within the brain called the striatum, which contains two sets of neural pathways: a "go" pathway, which incites an action, and a "stop" pathway, which inhibits action.

They found that both the go and stop pathways were stronger in habit-driven mice. Habit formation also shifted the relative timing of the two pathways, making the go pathway fire before the stop.

In the current study, the team wanted to understand the circuitry that coordinates these various long lasting changes in the brain. They had a hunch that a single type of rare cell in the striatum called the fast-spiking interneuron (FSI) might serve as master conductor of the widespread changes in the outgoing neurons' activity.

The FSI belongs to a class neurons responsible for relaying messages locally between other types of neurons in a particular brain region. Though FSIs make up about only one percent of the cells in the striatum, they grow long branch-like tendrils that link them up to the 95 percent of neurons that trigger the stop and go pathways.

"We were trying to put these pieces of the puzzle into a mechanism," Calakos said. "And we thought because of the way that fast-spiking interneurons are connected up to the other cells, it could be the one cell that is driving these changes in all of them. That is what we set about testing."

To test whether FSIs are truly the conductors of this cellular orchestra when it comes to habit, a graduate student in Calakos' lab, Justin O'Hare led the effort to take a closer look at the brain activity in lever-pressing mice. He found that forming a habit appeared to make the FSIs more excitable. He then gave the mice a drug that decreases the firing of FSIs, and found that the stop and go pathways reverted to their "pre-habit" brain activity patterns, and the habit behavior disappeared.

"Some harmful behaviors like compulsion and addiction in humans might involve corruption of the normally adaptive habit-learning mechanisms." Calakos said, "Understanding the neurological mechanisms underlying our habits may inspire new ways to treat these conditions."

"I firmly believe that to develop new therapies to help people, we need to understand how the brain normally works, and then compare it to what the 'broken' brain looks like," Calakos said.

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A digital version of this release is available at: https://today.duke.edu/2017/09/one-powerful-cell-makes-or-breaks-your-habits

This research was supported by the National Institutes of Health (NS064577, ARRA supplement to NS064577, AA021075, GM008441-23, NS051156 and DA040701), the McKnight Foundation, The Brain and Behavior Foundation, The Tourette Association of America and the Ruth K. Broad Foundation.

CITATION: "Striatal fast-spiking interneurons selectively modulate circuit output and are required for habitual behavior," Justin K. O'Hare, Haofang Li, Namsoo Kim, Erin Gaidis, Kristen Ade, Jeff Beck, Henry Yin and Nicole Calakos. *eLife*, Sept. 5, 2017. DOI: # 10.7554/eLife.26231

目次に戻る

5. 寄生虫の病原性の程度は、発生時期によって異なる -マウス実験

2017 年 9 月 8 日

我々の身体は内部時計の時間帯によって異なる働きをすることが知られているが、今回 McGill University と Douglas Mental Health University Institute の研究者らは、寄生虫感染もこれらの時計によって制御されることをマウス実験によって立証した。
同一チームの以前の研究において、免疫システムに独自の生物時計があることが示されていたが、今回マウスに寄生虫が注射されたとき、免疫反応が感染の時間によって大きく異なることを示した。これによると、リーシュマニア症においては、皮肉にも寄生虫に対する免疫反応が最も強力な早晩が感染にはより効果的であった。
研究者らは、概日時計がリーシュマニア感染をどのように制御しているかを更に理解することで、新しい治療法の開発やより良い予防アプローチに貢献することができる、としている。

英文記事：
https://www.sciencedaily.com/releases/2017/09/170908205417.htm

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Meeting a microbe in the morning or in the evening: Is it all the same?

Severity of a parasite's virulence depends on what time infection occurs

Date:

September 8, 2017

Source:

McGill University

Summary:

Does the time of day matter when our body is infected by a parasite? According to new research, it matters a great deal.

FULL STORY

Does the time of day matter when our body is infected by a parasite? According to new research from McGill University, it matters a great deal.

Our body works differently at different times of the day following our internal clocks. Researchers from McGill University and the Douglas Mental Health University Institute have now established that parasitic infections are also controlled by these clocks. The severity of a microbe's infection will thus vary whether it is encountered during the day or at night, a discovery that scientists believe could pave the way to new treatment and prevention strategies for parasitic infections.

Nicolas Cermakian, a professor at McGill's Department of Psychiatry and researcher at the Douglas Institute, made the discovery using Leishmania, a parasite that causes leishmaniasis and that is transmitted at night by the female sandfly. Every year, Leishmania infects about 1 million people, killing thousands and leaving many others with scars. Although the parasite is mostly located in tropical areas, climate change could spread Leishmania far beyond where it is found today. The parasite has already spread to certain parts of southern Europe.

When mice were injected with the parasite, Professor Cermakian's team discovered that their immune response varied greatly depending on what time of day the infection occurred.

"Our previous work showed that our immune system has its own biological clocks. Our body's defence mechanisms are more or less active at different times of the day," says Nicolas Cermakian, lead author of the new study published in Scientific Reports in collaboration with McGill/RI-MUHC Professor Martin Olivier and Professor Nathalie Labrecque of Université de Montréal and Maisonneuve-Rosemont Hospital research centre.

Silke Kiessling, a former postdoctoral student in Professor Cermakian's lab, found that Leishmania's infection was more effective in the early night, a time when the immune response to the parasite was the strongest.

But why would the parasite be transmitted by a fly that bites at the exact time when our defences are at their strongest? Simply put, the parasite thrives when it elicits a strong immune response, attracting inflammatory cells it uses to multiply (macrophages and neutrophils) to the infection site.

"We already knew that viral and bacterial infections were controlled by our immune system's circadian rhythms, but this is the first time this is shown for a parasitic infection, and for a vector-transmitted infection," Professor Cermakian adds.

Tools for better treatment and prevention

Professor Cermakian's team will now try to better define how Leishmania's circadian rhythm is controlled at the molecular and cellular levels. As a first step, they already found that the clock within cells of the immune system is directing the daily rhythm of response to Leishmania.

A better understanding of how the circadian clock controls Leishmania infection could contribute to the development of new therapeutics and better prevention approaches. Working out how time regulation of host-parasite interactions are controlled, Cermakian says, might also be useful in the fight against other diseases transmitted by insects.

Story Source:

Materials provided by **McGill University**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Silke Kiessling, Geneviève Dubeau-Laramée, Hyejee Ohm, Nathalie Labrecque, Martin Olivier, Nicolas Cermakian. **The circadian clock in immune cells controls the magnitude of Leishmania parasite infection**. *Scientific Reports*, 2017; 7 (1) DOI: 10.1038/s41598-017-11297-8

目次に戻る

6. 父親も子孫の性別に影響 -マウス研究

2017 年 9 月 11 日

哺乳動物では、伝統的に、母親だけが子孫の性別に影響を与えることができると考えられてきた。しかし、オックスフォード大学による野生のマウスを使った新しい研究によると、実際には父親が性別に影響を与えることが示されている。
この英国、スペイン、米国の共同研究は、*Proceedings of the Royal Society B* 誌に掲載されている。

英文記事：
https://www.sciencedaily.com/releases/2017/09/170911122602.htm

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Fathers can influence the sex of their offspring, scientists show

Date:

September 11, 2017

Source:

University of Oxford

Summary:

It has traditionally been thought that in mammals only mothers are able to influence the sex of their offspring. But a new study in wild mice has shown that fathers can, in fact, influence sex ratios.

FULL STORY

It has traditionally been thought that in mammals only mothers are able to influence the sex of their offspring.

But a new study in wild mice led by Dr Aurelio Malo of Oxford University's Department of Zoology has shown that fathers can, in fact, influence sex ratios.

The paper is published in the journal *Proceedings of the Royal Society B* and involves researchers from the UK, Spain and the USA.

Dr Malo said: 'In mammals, theory predicts that offspring sex ratios can only be determined by the mother, as fathers have always been thought to inseminate an equal proportion of X and Y sperm, having a random effect on offspring sex that they could not shift from equality, or 50:50.

'Also, mothers can influence their offspring in a number of ways from copulation to birth, whereas fathers have control over sperm only. This gives mothers more scope to alter the sex ratio of their offspring. The physical costs of gestation are obviously higher for the mother, so it's in her own interests from an evolutionary point of view to invest her resources wisely in terms of the sex, size and quality of her offspring.

'Using a wild rodent model -- the white-footed mouse -- in lab conditions, we found that there is a relationship between a father's genetic quality and the proportion of sons and daughters he has. We then showed that this relationship is mediated by a trait that is exclusive to the father: the size of the nuclei in their sperm, which reflects the proportion of X to Y sperm. Fathers with higher genetic quality produce sperm with smaller head nuclei -- a higher proportion of Y sperm -- and go on to produce more sons than daughters.

'The implications are important, as we now have the proof that fathers matter independently of any maternal effects. Scientists can now improve their predictive models of sex ratios at birth, including not only mothers but also fathers.'

The researchers also provide an adaptive explanation for why it's in the father's interests to alter the probability of having sons or daughters. According to Dr Malo, one plausible reason is that males of lower genetic quality minimise the cost of having sons, which are more susceptible to the negative

effects of inbreeding on fertility, by shifting the sex ratio to daughters, which are more resilient to these negative effects of inbreeding.

Dr Malo added: 'Using a wild species and not a domestic model such as lab mice allows us to extrapolate to other wild species, and to make inferences about adaptation -- that is, why natural selection has selected for this ability in fathers. These findings are potentially applicable to any other mammalian species, including our own. However, the extent to which we find the effects uncovered here depends very much on the mating systems. For instance, in more monogamous species the expectation that fathers would evolve an ability to manipulate sex ratios in their own interests is less clear.

'Predicting sex ratios has great interest for humans, as well as bioethical implications. In domestic species, such as livestock and pets, the ability to manipulate sex ratios has important economic implications. In endangered species, skewed population sex ratios can push species to the brink of extinction, so breeding programmes could pair males and females according to individual attributes that help achieve the rarer sex at birth.

'The long-held expectation that fathers would inseminate the same proportion of X and Y sperm generated at meiosis has stopped scientists from exploring paternal effects in other mammals. By showing that fathers can adjust sex ratios by varying sperm types, we help open the gates of a new research area of paternal effects on sex ratios. For example, do mothers and fathers have the same or opposing sex allocation interests? Does this vary across species and contexts?

'In a nutshell, we now know that dads, as well as mums, can alter the sex of their offspring, and that the ability to do so might have evolved through natural selection.'

Story Source:

Materials provided by **University of Oxford**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Aurelio F. Malo, Felipe Martinez-Pastor, Francisco Garcia-Gonzalez, Julián Garde, Jonathan D. Ballou, Robert C. Lacy. **A father effect explains sex-ratio bias**. *Proceedings of the Royal Society B: Biological Sciences*, 2017; 284 (1861): 20171159 DOI: 10.1098/rspb.2017.1159

目次に戻る

7. ヒトの躁鬱行動の特徴を有する遺伝子改変マウス

2017 年 9 月 18 日

ジョンズホプキンス大学の研究者らは、9 月 11 日に米国科学アカデミー紀要のオンライン版に掲載された報告の中で、ヒトの双極性障害の行動的特徴の多くを示す遺伝子改変マウスを使用して、そのマウスがリチウムのような双極性障害用に充分確立された薬物治療によって、異常行動を逆転することができた、としている。
研究者らは、この研究により、ヒトの双極性障害リスクに関連する遺伝子が脳の神経回路をどのように変化させるかについての科学的理解を促進し、新しい治療法を試験するための動物モデルが提供される可能性について力説している。

英文記事：
https://medicalxpress.com/news/2017-09-genetically-mice-hallmarks-human-bipolar.html

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Genetically altered mice bear some hallmarks of human bipolar behavior

September 18, 2017

Credit: Martha Sexton/public domain

Johns Hopkins researchers report they have genetically engineered mice that display many of the behavioral hallmarks of human bipolar disorder, and that the abnormal behaviors the rodents show can be reversed using well-established drug treatments for bipolar disorder, such as lithium.

Specifically, the mice lacked the protein ankyrin-G, in particular neurons in the brain, a defect that appears to make the animals both hyperactive and less fearful, a behavioral profile suggestive of a mania-like state for a mouse. At the same time, the rodents had an even greater response to social defeat stress than normal mice do, suggesting their brains also are more susceptible to a depressive-like state. Human bipolar disease is characterized by swings in "manic" and "depressive" moods.

In a report on the mouse studies, published online Sept. 11 in *PNAS*, the investigators say the genetic alteration appears to release the biochemical "brakes" on brain cells involved in body movement, reasoning and perception of the world, triggering over-excited activity and reactions.

The results of their work, the researchers say, may advance scientific understanding of how genes linked to the risk of human bipolar disorder change neuronal circuits in the brain, and may offer an animal model for testing new treatments. Bipolar disorder is estimated to affect about 5.7 million people, or 2.6 percent of adults in the United States, according the National Institute of Mental Health.

"Mouse behavior isn't the same as human behavior, so we need to be cautious, but we were surprised and heartened by the fact that the mutant mice responded to lithium treatment—a gold standard for treating human bipolar disorder and alleviating features of mania and depression," says Christopher Ross, M.D., Ph.D., professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. "To our knowledge, this is the first robust mouse model of bipolar disorder based on a genome-wide significant risk factor for the human disorder." Ross points out that mouse disease models are still unusual in psychiatry, even though with careful interpretation they have proved to be important for understanding and treating many diseases.

Because the gene for Ankyrin-G has popped up in several genome-wide association studies combing human DNA for genetic risk factors of bipolar disorder, the researchers focused their attention on its role in the brain. Their collaborators—Paul Jenkins, Ph.D., and Vann Bennett, M.D., Ph.D., then at Duke University Medical Center—had tried creating a mouse mutant completely lacking the ankyrin-G protein, but the mice didn't survive because ankyrin-G seems to be required for nervous system development.

To circumvent that problem, the researchers generated their new mouse so that ankyrin-G would only be lost in the pyramidal neurons found in the front of the brain (the region believed to be most relevant for psychiatric disorders) in adolescent and adult mice.

To see if the loss of ankyrin-G in the pyramidal neurons changed the animals' behavior, the researchers used tests including a so-called "open field" test to see how the mice acted when placed in an empty chamber. Normal mice tend to hug the walls and not venture out into open space, but the ankyrin-G mutant mice were more active and spent much more time in the open part of the space.

At their most active, each normal mice ventured near the middle of the chamber on average 9,000 times per hour, whereas each mutant mice ventured near the middle more than 20,000 times per hour. The mutant mice were also overall more active for longer periods—up to 20 hours compared to the typical 12 hours for normal mice. Mice are nocturnal, meaning that in the wild, they tend to be more active at night.

In order to exclude the possibility that the hyperactive mutant mice were displaying symptoms of attention deficit hyperactive disorder (ADHD), the researchers gave the mice methylphenidate—a drug that calms those with ADHD but makes those without ADHD even more excitable—in doses of either 10 or 30 milligrams per kilogram of body weight. After 25 minutes, the researchers tested them in the open field test. The drug made the ankyrin-G mutant mice more hyperactive, indicating they did not have "mouse-ADHD."

Ross says that because the hyperactivity and decreased anxiety might be interpreted as "mania-like" symptoms, the researchers fed the mice either lithium or valproic acid (an anti-seizure drug, also used to treat mania) over a two week period, as is often done in human therapeutic trials. They verified that blood concentration levels were comparable to effective levels in humans being treated for bipolar disorder or mania, and then administered the open field and other behavioral tests. Remarkably, the activity levels of ankyrin-G mutant mice given the drugs returned to those of the controls.

In people with bipolar disorder, mania seems to occur spontaneously, but depression often tends to happen after some sort of trigger or stressor, Ross notes. To see if the mutant mice developed depressive-like traits under those conditions, the researchers stressed the ankyrin-G mice by placing them with a bigger, "bully" mouse for daily sessions over two weeks. Researchers then gave the mice several behavioral tests for

"depression" including the forced swim test, in which researchers measure how fast the mice give up swimming and decide to float.

In baseline tests, the high-energy ankyrin-G mice usually swam longer, only floating for about 10 seconds of the 200 second test compared to the normal mice that floated about 50 seconds, but after several sessions with the bully mice, the ankyrin-G mice were quick to give up and float, remaining still for well over 100 seconds on average.

"One way to interpret these results is that the mutant mice were quick to give in to defeat after feeling bullied, and switched to a depressive-like state, which was the opposite of their hyperactive, less-anxious norm," says Shanshan Zhu, Ph.D., lead author and researcher in Ross' lab.

Ankyrin-G is normally found in pyramidal neurons in the brain of mammals, including people. The neurons are responsible for many of the key functions that the brain controls, sending nerve pulses that ultimately result in movement and cognition. To see what was happening in the brains of these ankyrin-G mutant mice, the researchers analyzed the cell components in inhibitory synapses connecting with pyramidal neurons, finding that two proteins known as GAT1 and GAD67—responsible for making the neurochemical GABA that dials back nerve impulses—were at much lower levels in the synapses on pyramidal neurons in ankyrin-G mutant mice than in normal mice. The experiments are consistent with the idea, Zhu says, that the pyramidal neurons in the mutants seem to be hyperactive.

"What we found at the cellular level correlates with the behaviors we saw in the less-anxious, hyper-active mice, which means having overactive pyramidal neurons with their brakes removed could be contributing to these behaviors," says Zhu.

The research group hopes to use its ankyrin-G mice to better understand the biology of bipolar disorder, to help clarify how lithium works to treat bipolar disorder, and to test new treatments for bipolar disorder.

Explore further: Bipolar disorder and epilepsy linked to turning down an inhibitory switch in brain circuits

More information: Shanshan Zhu et al. Genetic disruption of ankyrin-G in adult mouse forebrain causes cortical synapse alteration and behavior reminiscent of bipolar disorder, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1700689114

Journal reference: Proceedings of the National Academy of Sciences

Provided by: Johns Hopkins University School of Medicine

目次に戻る

8. 脂肪を溶かす貼り薬、人に応用可の期待 -マウス実験で開発

2017 年 9 月 18 日

【AFP＝時事】米国の研究者らがマウスを使った実験で、脂肪を溶かすスキンパッチ（貼り薬）の開発に成功したと発表した。人の肥満や糖尿病治療にも応用可能かどうか、今後の研究で探っていく。

米国化学会（American Chemical Society）発行の学術誌「ACS Nano」に 15 日発表された論文によると、このスキンパッチはナノテクノロジーを利用して体内の代謝を上げ、エネルギーを蓄積する白色脂肪を、エネルギーを燃焼する褐色脂肪へと変化させることができる。マウスを使った 4 週間の実験では、スキンパッチが貼られた部分の脂肪が 20%減少した。

論文の共同執筆者で、米コロンビア大学メディカルセンター（Columbia University Medical Center）病理・細胞生物学部のリー・チャン（Li Qiang）准教授は、「腹部のぜい肉を減らす脂肪吸引の代替手段として非侵襲性の治療が可能になるかもしれないと分かれば、間違いなく多くの人が興奮を覚えるだろう」と語った。

薬の成分は人の髪の毛の 400 分の 1 ほどの細さに相当する直径約 250 ナノメートル（1 ナノメートル＝100 万分の 1 ミリ）のナノ粒子に入れられている。皮膚に刺さる微細な針数十本が付いた指先大のスキンパッチに、これらのナノ粒子が仕込まれている。

ノースカロライナ大学チャペルヒル校（University of North Carolina at Chapel Hill）とノースカロライナ州立大学（North Carolina State University）合同の医用生体工学部准教授で、スキンパッチの設計を担当したゼン・グ（Zhen Gu）氏によると、このパッチの仕組みにより、薬の成分は「全身に素早く行き渡るのではなく、持続的に」組織付近へと浸透させ

ることができるという。

実験は 4 週間行われ、マウスの腹部に貼られたパッチは 3 日ごとに交換されたという。

【翻訳編集】AFPBB News

http://www.afpbb.com/articles/-/3143315

英文記事：

https://www.sciencedaily.com/releases/2017/09/170915095206.htm

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Skin patch dissolves 'love handles' in mice

Microneedle skin patch that delivers fat-shrinking drug locally could be used to treat obesity and diabetes

Date:

September 15, 2017

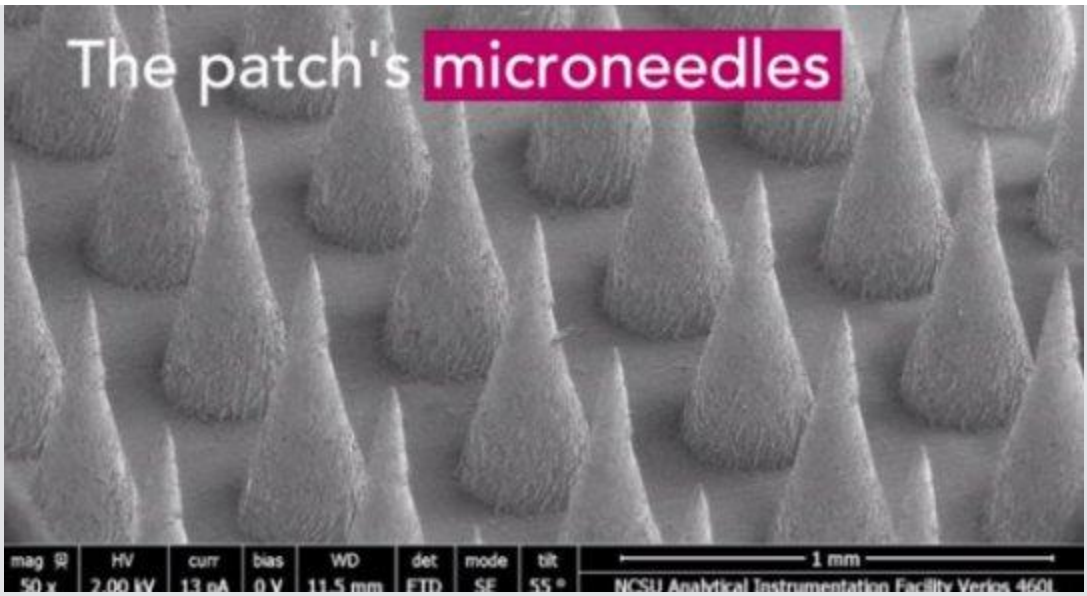
Source:

Columbia University Medical Center

Summary:

Researchers have developed a medicated skin patch that can turn energy-storing white fat into energy-burning brown fat locally while raising the body's metabolism. The patch could be used to burn off pockets of unwanted fat and treat metabolic disorders like obesity and diabetes.

FULL STORY



Microneedle patch.

Credit: Zhen Gu, UNC and NC State

Researchers have devised a medicated skin patch that can turn energy-storing white fat into energy-burning brown fat locally while raising the body's overall metabolism. The patch could be used to burn off pockets of unwanted fat such as "love handles" and treat metabolic disorders like obesity and diabetes, according to researchers at Columbia University Medical Center (CUMC) and the University of North Carolina.

The findings, from experiments in mice, were published online in *ACS Nano*.

Humans have two types of fat. White fat stores excess energy in large triglyceride droplets. Brown fat has smaller droplets and a high number of mitochondria that burn fat to produce heat. Newborns have a relative abundance of brown fat, which protects against exposure to cold temperatures. But by adulthood, most brown fat is lost.

For years, researchers have been searching for therapies that can transform an adult's white fat into brown fat -- a process named browning -- which can happen naturally when the body is exposed to cold temperatures -- as a treatment for obesity and diabetes.

"There are several clinically available drugs that promote browning, but all must be given as pills or injections," said study co-leader Li Qiang, PhD, assistant professor of pathology and cell biology at CUMC. "This exposes the whole body to the drugs, which can lead to side effects such as stomach upset, weight gain, and bone fractures. Our skin patch appears to alleviate these complications by delivering most drugs directly to fat tissue."

To apply the treatment, the drugs are first encased in nanoparticles, each roughly 250 nanometers (nm) in diameter -- too small to be seen by the naked eye. (In comparison, a human hair is about 100,000 nm wide.) The nanoparticles are then loaded into a centimeter-square skin patch containing dozens of microscopic needles. When applied to skin, the needles painlessly pierce the skin and gradually release the drug from nanoparticles into underlying tissue.

"The nanoparticles were designed to effectively hold the drug and then gradually collapse, releasing it into nearby tissue in a sustained way instead of spreading the drug throughout the body quickly," said patch designer and study co-leader Zhen Gu, PhD, associate professor of joint biomedical engineering at the University of North Carolina at Chapel Hill and North Carolina State University.

The new treatment approach was tested in obese mice by loading the nanoparticles with one of two compounds known to promote browning: rosiglitazone (Avandia) or beta-adrenergic receptor agonist (CL 316243) that works well in mice but not in humans. Each mouse was given two patches -- one loaded with drug-containing nanoparticles and another without drug -- that were placed on either side of the lower abdomen. New patches were applied every three days for a total of four weeks. Control mice were also given two empty patches.

Mice treated with either of the two drugs had a 20 percent reduction in fat on the treated side compared to the untreated side. They also had significantly lower fasting blood glucose levels than untreated mice.

Tests in normal, lean mice revealed that treatment with either of the two drugs increased the animals' oxygen consumption (a measure of overall metabolic activity) by about 20 percent compared to untreated controls.

Genetic analyses revealed that the treated side contained more genes associated with brown fat than on the untreated side, suggesting that the observed metabolic changes and fat reduction were due to an increase in browning in the treated mice.

"Many people will no doubt be excited to learn that we may be able to offer a noninvasive alternative to liposuction for reducing love handles," says Dr. Qiang. "What's much more important is that our patch may provide a safe and effective means of treating obesity and related metabolic disorders such as diabetes."

The patch has not been tested in humans. The researchers are currently studying which drugs, or combination of drugs, work best to promote localized browning and increase overall metabolism.

Video: https://www.youtube.com/watch?v=uBHNeLoiuwo

Story Source:

Materials provided by **Columbia University Medical Center**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yuqi Zhang, Qiongming Liu, Jicheng Yu, Shuangjiang Yu, Jinqiang Wang, Li Qiang, Zhen Gu. **Locally Induced Adipose Tissue Browning by Microneedle Patch for Obesity Treatment**. *ACS Nano*, 2017; DOI: 10.1021/acsnano.7b04348

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- MLA
- APA
- Chicago

Columbia University Medical Center. "Skin patch dissolves 'love handles' in mice: Microneedle skin patch that delivers fat-shrinking drug locally could be used to treat obesity and diabetes." ScienceDaily. ScienceDaily, 15 September 2017. <www.sciencedaily.com/releases/2017/09/170915095206.htm>.

Columbia University Medical Center. (2017, September 15). Skin patch dissolves 'love handles' in mice: Microneedle skin patch that delivers fat-shrinking drug locally could be used to treat obesity and diabetes. *ScienceDaily*. Retrieved September 19, 2017 from www.sciencedaily.com/releases/2017/09/170915095206.htm

Columbia University Medical Center. "Skin patch dissolves 'love handles' in mice: Microneedle skin patch that delivers fat-shrinking drug locally could be used to treat obesity and diabetes." ScienceDaily. www.sciencedaily.com/releases/2017/09/170915095206.htm (accessed September 19, 2017).

目次に戻る

9. アルコール摂取起因の肝臓問題には食事が重要な役割

2017 年 9 月 25 日

Alcohol and Alcoholism 誌に掲載された新しい研究において、多量のアルコールを摂取しながらも食事によって制御されているマウスは必ずしも最重度の肝障害を発症するとは限らず、食事が肝障害発症に重要な役割を果たすことが示唆されている。
アルコール性肝疾患は世界的な健康負担であり、肝腫および単純な脂肪肝から、アルコール性脂肪性肝炎および肝硬変などより重篤な病状に至る病気である。アメリカでは、人口の約半分がアルコールを飲んでおり、約 3,800 万人が過飲傾向にあるとされている。
この研究では、多量のアルコールを優先的に摂取するように飼育された（cHAP）マウスと慢性的にエタノールを過摂取するマウスモデルを比較しながら、アルコール性肝疾患を誘発させた。マウスは 4 週間にわたって異なる食事を与えられたが、消費されたアルコールの総量以外の要因が、アルコール性肝疾患発症の程度に影響を及ぼすことが示された、としている。

英文記事：
https://www.eurekalert.org/pub_releases/2017-09/oupu-dia092517.php

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PUBLIC RELEASE: 25-SEP-2017

Diet, in addition to alcohol consumption, may play important role in liver problems

OXFORD UNIVERSITY PRESS USA

A new study published in *Alcohol and Alcoholism* finds that mice bred to consume high amounts of alcohol, but controlled by diet, did not necessarily develop the most severe liver injuries, suggesting that diet may pay an important role in liver injury development.

Alcoholic liver disease is a global health burden and refers to a disease spectrum ranging from hepatomegaly and simple fatty liver (hepatic steatosis), to more severe pathologies such as alcoholic steatohepatitis and hepatic cirrhosis. In the United States about half of the population drinks alcohol and approximately 38 million people are estimated to engage in binge drinking behavior.

This study sought to compare mice bred to preferentially consume high amounts of alcohol (crossed-High Alcohol Preferring, or cHAP, mice) to other mice using a chronic-binge ethanol ingestion model to induce alcoholic liver disease.

The mice were randomized and given different diets over a four-week period. Researchers collected tissue and serum. The researchers discovered that the cHAP mice on a diet of alcohol and water consumed significantly more alcohol than cHAP or other mice maintained on an alcohol diet. However, cHAP and other mice on the alcohol diet together with the artificial sugar maltodextrin had greater hepatosteatosis and overall degree of liver injury compared to mice that consumed a diet of alcohol and water together with maltodextrin.

These data suggest factors other than total amount of alcohol consumed may affect the degree of alcoholic liver disease development.

Additionally, because cHAP mice exhibit increasing ethanol consumption over time, consume ethanol in parallel with normal dietary intake, and show higher levels of daily ethanol consumption than mice maintained on the controlled diet, this model may provide an additional rodent model to study the effects of ethanol on hepatic pathology that more closely mimics human patterns of ethanol consumption in heavy drinkers.

In discussing these outcomes, the authors speculated saturated fat in the diet of the standard rodent chow used, and/or epigenetic changes during strain development, may have accounted for lack of liver injury.

This position is corroborated by studies demonstrating a protective role for saturated fats in chronic ethanol-fed rodents in which diminished inflammation and decreased micro- and macrovesicular steatosis occurs to promote hepatic fatty oxidation. Saturated fats may also inhibit the development of alcoholic liver disease by maintaining growth of intestinal microbiota.

The findings suggest that although cHAP mice consume consistently high/sustained levels of ethanol, other factors such as disparities in specific dietary components, differences in the patterns of alcohol consumption, and timing of feeding relative to peak blood-alcohol content, alter the degree of liver injury in cHAP versus other mice.

"The detrimental effects of sustained heavy alcohol intake on liver health is well established. However, animal models of alcohol-induced liver injury that replicate the human disease are more difficult to establish. Our collaborators at IUPUI have developed a mouse model of alcohol intake that mirrors many of the characteristics of human alcohol consumption, in which mice given the choice between water and alcohol preferentially choose alcohol, said the paper's lead author, Iain H. McKillop, Ph.D. "Our data report that while cHAP mice drink more total alcohol than other models, the resulting degree of liver injury was less. These results suggest that other factors, such as dietary composition and/or genetic breeding leading to greater hepatic tolerance to alcoholic liver injury, may be involved. Translating these data to human studies, to understand the differing effects of alcohol consumption and patterns of drinking on the development and progression of liver disease may identify risk factors other than total alcohol consumed for developing liver disease."

"A critical role of the gut microbiome and fecal metabolites is becoming increasingly Appreciated," wrote Irina Kirpich and Craig McClain in an editorial accompanying the study. Marked differences in the composition of the diets used in this study may help explain why mice consuming the highest amounts of alcohol did not develop the most severe liver injury. Diet and microbiome may be important variables in the different outcomes observed in various experimental alcoholic liver disease models."

###

The paper "Use of a Crossed High-Alcohol Preferring (cHAP) Mouse Model with the NIAA-Model of Chronic-Binge Ethanol Intake to Study Liver Injury" is available at: https://academic.oup.com/alcalc/article/doi/10.1093/alcalc/agx063/4191311/Use-of-a-crossed-high-alcohol-preferring-cHAP

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目次に戻る

10. 幹細胞の水分量が脂肪になるか骨になるかを決める

2017 年 9 月 26 日

幹細胞に水分を加えたり、また幹細胞から水分を取り除いたりすることで、脂肪細胞か前骨細胞のいずれかに変わる可能性がある、という新たな研究が発見された。
この研究では、細胞の体積を変化させることによって、外面を覆うマトリックスの剛性を含む内部ダイナミクスが変化することを発見。幹細胞においては、水分を除去すると細胞が凝縮し硬骨前骨細胞になり、水分を加えると細胞が膨潤して柔らかい前脂肪細胞が形成された。
バッファロー大学、マサチューセッツ工科大学、ハーバード大学によるこの共同研究は米国科学アカデミー紀要に掲載され、再生医療のための幹細胞生物学の理解と利用に新しいツールを追加するものだ、としている。

英文記事：
https://www.sciencedaily.com/releases/2017/09/170926125131.htm

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Amount of water in stem cells can determine its fate as fat or bone

Study is first to find cell volume can influence the future role of stem cells, regardless of environment

Date:

September 26, 2017

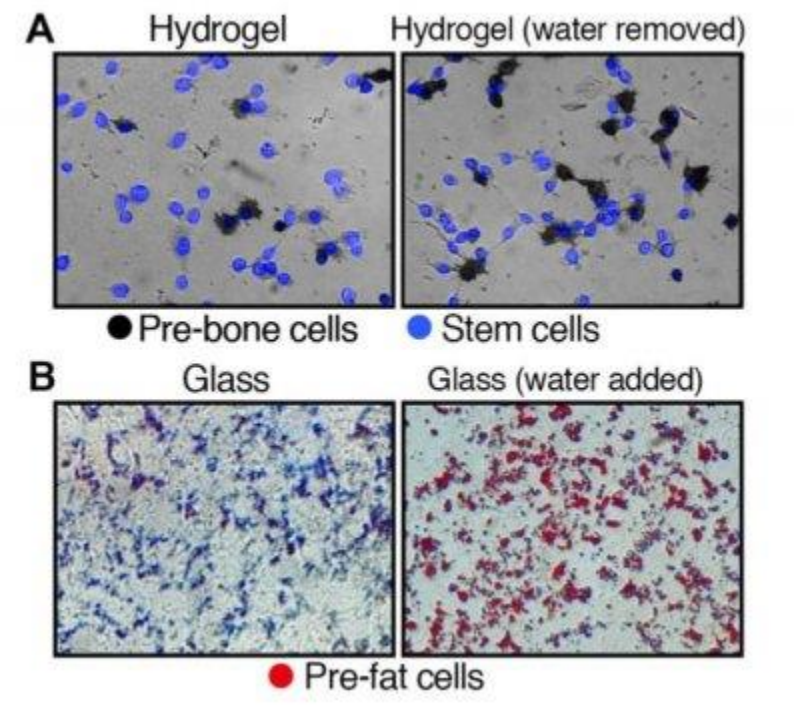
Source:

University at Buffalo

Summary:

Adding or removing water from a stem cell can change the destiny of the cell to either pre-fat cells or pre-bone cells, researchers have discovered in a new study.

FULL STORY



Top images (A): Illustrates the development of stem cells on hydrogel, a soft substrate, to pre-bone cells after the removal of water. Bottom images (B): Depicts the development of stem cells on glass, a hard substrate, to pre-fat cells after the addition of water.

Credit: Courtesy of the researchers

Adding or removing water from a stem cell can change the destiny of the cell, researchers have discovered in a new study published in the *Proceedings of the National Academy of Sciences* of the United States of America (PNAS).

The research found that altering the volume of a cell changed its internal dynamics, including the rigidness of the matrix lining the outer surface. In stem cells, removing water condenses the cell, influencing the stem cells to become stiff pre-bone cells, while adding water causes the cells to swell, forming soft pre-fat cells.

Researchers have long understood that stem cells are influenced by the cells around them, picking up cues on what their function should be based on the stiffness of the matrices of neighboring cells.

The results, however, confirm that nature plays as much of a role as nurture in stem cell behavior and development.

"The findings from this study add a fascinating new tool to our understanding and utilization of stem cell biology for regenerative medicine," says Praveen Arany, DDS, PhD, co-author and assistant professor in the Department of Oral Biology in the University at Buffalo School of Dental Medicine.

The study was led by Ming Guo, PhD, d'Arbeloff Assistant Professor in the Department of Mechanical Engineering at the Massachusetts Institute of Technology; and David Weitz, PhD, Mallinckrodt Professor of Physics and of Applied Physics in the John A. Paulson School of Engineering and Applied Sciences at Harvard University.

"For the first time, we're beginning to understand the importance of cell volume and cellular water content in the mechanical properties and physiological functions of cells," says Guo, who began the research as a graduate student in Weitz's lab at Harvard.

The Line Between Bone and Fat

The research originally sought to understand the effects of volume on a cell's characteristics and functions. Cell volume is highly regulated and changes frequently over the course of a cell's life, increasing as the cell grows and decreasing when it divides.

These changes in volume are a result of variations in the amount of protein, DNA and other materials within the cell, though they mostly remain constant. But cells can also experience rapid and extreme

changes in size and density through the absorption or release of water, spreading or shrinking in as little as 20 minutes.

By increasing or decreasing the volume of cells by 20 percent, the investigators found that the cells experienced several internal changes, including in gene expression and stiffness.

Knowing the role cell stiffness plays in the development of stem cells, the researchers began to wonder if cell volume could affect their fate as well.

To test the premise, investigators placed stem cells at their normal volume in a hardened hydrogel substrate to simulate the rigidness of bone cells. After one week, a large portion of the stem cells developed into pre-bone cells.

The experiment was repeated with a softened hydrogel substrate. In the softer environment, there was a significant decrease in the number of stem cells that became pre-bone cells. However, when water was removed from the cells to decrease their volume by 20 percent, the number of stem cells that became pre-bone cells increased, despite being in the softer substrate.

A similar experiment was conducted using glass. Researchers placed stem cells on glass to simulate a stiffer environment and found that few of the cells developed into pre-fat cells. It was not until the volume of the stem cells was increased by 20 percent that a spike in the formation of fat cells was found.

The investigators discovered that changing the volume of the cells caused them to behave similarly to as if they were under environmental pressures.

"The surprising thing about these experiments is the observation that volume seems to be related to so much about the cell. It seems to dictate the cell stiffness as well as the cell fate," says Weitz, also a core faculty member of the Wyss Institute for Biologically Inspired Engineering and director of the Materials Research Science and Engineering Center at Harvard.

"These observations may also have implications in external means of monitoring cell fate, which may be important for future biotech applications."

Future studies are needed to examine the effects of varied changes in volume, as well as if cell volume or external cues are the dominating factor in the fate of stem cells.

The Future of Regenerative Medicine

Stem cells sit at the forefront of regenerative medicine, providing researchers and clinicians with the potential to repair or replace damaged tissue and organs.

With the ability to develop into any type of specialized cell -- from a muscle cell to a red blood or brain cell -- stem cells hold the potential to treat various diseases and conditions, from heart disease to tooth loss. Bone marrow transplantation, one form of stem cell therapy, is already in widespread use.

Stem cells may also aid in drug development and the understanding of how cancer and birth defects occur.

Learning what causes differentiation among these cells will help researchers generate methods that influence their behavior and, ultimately, develop new therapies.

Aside from physical cues such as cell stiffness or volume, stem cell differentiation can be influenced by a number of biological factors, pharmaceutical drugs or biophysical agents, such as light, ultrasound and radio frequencies.

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Journal Reference:

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