Bio News – June, 2023

In-Vivo Science International, Inc.

今月の企業関連ニュース/他

5/1　ナマケモノの毛皮に抗生物質生産菌か 耐性菌問題に光　コスタリカ

ナマケモノの毛皮に抗生物質生産菌が潜んでいる可能性があると、中米コスタリカの研究チームが発表した。近年深刻化している抗生物質が効かない「スーパー耐性菌」の問題に光をもたらすかもしれないと、研究者らは期待を寄せている。研究論文が学術誌エンバイロメンタル・マイクロバイオロジー（Environmental Microbiology）に掲載された。

5/1　大塚製薬/Lundbeck（本社：デンマーク）の 2 か月に 1 回投与の抗精神病薬 Abilify Asimtufii を FDA が承認

FDA Approves Otsuka and Lundbeck's ABILIFY ASIMTUFII® (aripiprazole), the First Once-Every-Two-Months Long-acting Injectable (LAI) for the Treatment of Schizophrenia or Maintenance Monotherapy Treatment of Bipolar I Disorder in Adults | Business Wire

5/2　米国承認審査段階の地図状萎縮薬を擁する Iveric Bio（本社：ニューヨーク州）をアステラス製薬が 59 億ドルで買収

Astellas to Buy Eye-Drug Maker Iveric Bio for $5.9 Billion (msn.com)

5/3　尿路結石のもとを分解菌に運ぶ分子、立体構造が明らかに 岡山大など

尿路結石のもとになるシュウ酸を分解する腸内細菌に存在し、シュウ酸を取り込む分子「シュウ酸輸送体」の立体構造を、岡山大学学術研究院医歯薬学域の山下敦子教授（構造生物学）らの研究グループが大型放射光施設 SPring-8 で解明した。小さな分子であるシュウ酸を柔らかく包みこみ、効率よく菌内に運んでいた。この働きを生かして腸内のシュウ酸を吸収・分解できれば、尿路結石症を防ぐことが期待される。

5/5　コロナ緊急事態宣言「終了」 WHO、3 年 3 カ月で節目

5/5　ネスレ（Nestle）、仏東部でのミネラルウオーター用採水停止 干ばつの影響で

5/6　ChatGPT、学習で大量 CO_2　AI と温暖化「不都合な真実」

画期的な性能で世界的に注目が集まる「ChatGPT（チャット GPT）」など生成 AI（人工知能）が、地球温暖化問題には悪影響を与えるかもしれない――そんな報告書を米スタンフォード大が 4 月に出した。AI 開発に使われる大量の電力による二酸化炭素排出量は、米国人の 1 年あたりの排出量の何十倍にもなると指摘。開発競争が激化する中、電力需要への対応や二酸化炭素の排出が少ない電源の確保が重要になりそうだ。

5/6　簡易プール販売禁止へ 南仏の渇水対策

フランス政府は 5 日、干ばつが続く南部で簡易プールの販売を禁止すると発表した。ピレネーオリアンタル（Pyrenees-Orientales）県のロドリゲ・フルシー（Rodrigue Furcy）知事によると、南仏の大部分は 1959 年以来、最も深刻な干ばつに見舞われている。

5/7　ミズアブの幼虫が生ゴミの臭いを軽減　腸内細菌に抑制効果か

茨城県つくば市の農業・食品産業技術総合研究機構（農研機構）などの研究チームは、ハエの仲間であるアメリカミズアブ（ミズアブ）の幼虫の力で生ごみの腐敗臭を抑制する技術を開発したと発表した。

5/7　光照射でがん細胞死滅、龍谷大など誘起メカニズム解明

龍谷大学の中川優磨大学院生（研究当時）や内田欣吾教授らは、光で可逆的に色が変わる性質を持つジアリールエテンが光の吸収により起こる異性化を経て細胞のデオキシリボ核酸（DNA）の塩基対間に挿入された後に、光照射することでヒトのがん細胞（HeLa 細胞）をアポトーシス（細胞死）させることを見いだした。薬剤に光スイッチ機能を追加することで、副作用や毒性が抑えられる薬剤の開発につながることが期待できる。
産業技術総合研究所、山梨大学との共同研究。研究チームはこれまでにジアリールエテン誘導体の存在下で青色光を照射してイヌ腎臓尿細管上皮細胞由来の細胞株を死滅させた実験で、カスパーゼの活性化がアポトーシスに関わっていたことなどを突き止めていた。これらの研究を踏まえてジアリールエテン分子がどのようにアポトーシスに関与するか、HeLA 細胞を使って確認することにした。DNA の塩基対間に挿入されたジアリールエテン分子が光照射を受けると開環・閉環反応を繰り返して DNA の 2 本鎖の両方を切断。細胞死に至ることがわかった。
成果は米化学会誌ジャーナル・オブ・メディシナル・ケミストリーに掲載された。

5/8　英国成人の 5 人に 1 人が不快な音をやり過ごせない音嫌悪症

5/9　マツタケのゲノム完全解読　生態の仕組み、解明期待　かずさ DNA 研と東大

マツタケの全遺伝情報（ゲノム）を完全解読し、約 2 万 1,900 個の遺伝子を特定したと、かずさ DNA 研究所（千葉県木更津市）と東京大の研究チームが 8 日発表した。
マツタケ特有の香りと味を生み出す遺伝子や、アカマツなどの根の周辺に生える詳しい仕組みを解明するのに役立つと期待される。論文は国際的な科学誌 DNA リサーチ電子版に掲載された。

5/10　飢餓から命守る肝臓の働き発見、糖尿病に応用も 東北大など

肝臓が飢餓を感じて血中に特別なタンパク質を放ち、カロリー消費を抑え、食欲を高める仕組みをマウスの実験で発見した。東北大学などの研究グループが発表した。
糖尿病患者で血糖値が高い時にこの仕組みが働くことも判明し、食べ過ぎを防ぐ治療につながる可能性があるという。
研究グループは東北大学、東京医科歯科大学、山形大学で構成。成果は米生命科学誌「セルリポーツ」に 4 月 28 日に掲載された。研究は日本学術振興会新学術領域研究、文部科学省科学研究費補助金、科学技術振興機構（JST）ムーンショット型研究開発事業の支援を受けた。

5/10　京大などが新種のエビ“発見”…その名は「ワカサムラサキエビ」透き通ってキレイ　京都府伊根沖の若狭湾で

5/10　3 人の DNA を持つ赤ちゃん、イギリスで初めて誕生

イギリスの保健当局はこのほど、同国で初めて、3 人の DNA を持つ赤ちゃんが誕生したと明らかにした。この赤ちゃんの DNA はほとんどが両親のものだが、別の女性提供者のものが約 0.1％含まれるという。当局は、3 人の DNA を使った赤ちゃんはこれまでに最大 5 人生まれているとしたが、それ以上の詳細は明らかにしていない。
この先端技術は、親から赤ちゃんにミトコンドリア病が伝わるのを防ぐことを目的としている。ミトコンドリア病は治療法がなく、出生後数時間から数日で死に至る可能性もある。この病気で子供を何人も失っている家族もあり、今回の技術は、そうした家族にとって健康的な子供を授かる唯一の手段とみられている。

5/11　Microsoft が「核融合の電力購入契約」を締結　2028 年までに米・核融合スタートアップが供給目指す

5/11　武田薬品がマサチューセッツ州の従業員最大 186 人を解雇

https://www.fiercebiotech.com/biotech/takeda-confirms-fallout-gene-therapy-rd-refocus-186-redundancies

5/11　FDA が招集した専門家がアイルランドの Perrigo の避妊薬 Opill 店頭販売の承認を支持

5/11　WHO、サル痘「緊急事態」終了　宣言から 10 カ月

5/12　アステラス製薬の閉経症状治療薬 Veozah を FDA が承認

https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-approves-astellas-pharmas-therapy-menopause-related-symptoms-2023-05-12/

5/12　武田薬品、Theravance（本社：カリフォルニア州サウスサンフランシスコ市）と Enterome（本社：フランス パリ）との提携打ち切りを決定

5/15　男女間の不平等、脳の厚さに影響 -京大など

男女間の不平等が大きい国ほど、脳の厚さの男女差が大きいことが、日本を含む世界の 29 カ国の共同研究でわかった。女性のメンタルヘルスの悪化などにつながっているおそれがあり、国際共同研究チームに加わった専門家は、具体的にどんな男女間の不平等が脳の発達に影響を与えているか、追跡調査が必要だと指摘している。京都大を含む研究チームが、世界 29 カ国の 18～40 歳の健康な男女 7,876 人の MRI による脳の構造画像と、男女間の不平等指標との関連を調べた。

5/15　ダイヤモンド半導体、トヨタ・デンソー共同設立会社とオーブレーが研究開始

Orbray（オーブレー、東京都足立区、並木里也子社長）とミライズテクノロジーズ（愛知県日進市、加藤良文社長）は 11 日、電気自動車（EV）など電動車向けダイヤモンド製パワー半導体の共同研究を始めたと発表した。
ダイヤモンドは耐電圧性能と熱伝導率に優れ、電動車への搭載で燃費・電費性能の向上が期待できる。カーボンニュートラル（温室効果ガス排出量実質ゼロ）に向けた電動車の普及拡大を見通し、10 年後の実用化を目指す考え。

5/16　環境中の人の DNA 抽出、解読　持ち主推定、倫理課題も

海や川の水、砂浜の足跡や室内の空気から人の DNA を抽出して遺伝情報を解読し、持ち主の体質や民族集団を推定することができたと、米フロリダ大などのチームが 15 日発表した。人は皮膚や唾液の飛散などを通じて知らないうちに環境中に遺伝情報をばらまいており、技術的には個人の特定も可能とみている。犯罪捜査や捜索救助活動への応用が見込める半面、少数民族の動向把握など同意なき監視に使われる恐れもあり「倫理的課題の検討を始めてほしい」と政策担当者らに呼びかけた。論文は英科学誌ネイチャー・エコロジー・アンド・エボリューションに掲載された。

5/16　赤ちゃんのアトピー、積極治療で「卵アレルギー抑制」の研究報告

アトピー性皮膚炎の赤ちゃんに、ステロイドの塗り薬を使って通常より積極的な治療をすると、卵アレルギーを発症する割合が減ったとする研究結果を、国立成育医療研究センター（東京都世田谷区）の研究グループが発表した。

5/15　ワサビの辛み成分が野菜や切り花の鮮度を保持　名大と関学大が発見

植物の葉などの表皮にある水分やガス交換の出入り口「気孔」が開くのを抑える天然の物質を、名古屋大や関西学院大の研究チームが見つけた。ワサビなどの辛み成分の一つで、葉野菜や切り花の鮮度保持などへの利用が期待されるという。
研究チームは、約 3 万種類の化合物を探索できるシステムを使って、ベンジルイソチオシアネート（BITC）という天然の物質が、気孔が開くのを抑制する効果が高いことを見いだした。BITC はアブラナの仲間の植物が細菌などから身を守るためにつくる。ワサビやマスタードの辛み成分の一つで、抗菌・防カビ剤としても利用されてきた物質だ。気孔は周囲にある孔辺細胞の体積が増えると開く。BITC はこの細胞の膜にあるポンプのような部分が働くのを抑制することもわかった。実際に BITC を切り花のキクの葉に直接塗ると、しおれるのを通常よりも抑制することを確認できた。

5/16　コロナ薬レムデシビルの副作用の仕組み解明、改善に期待　東北大など

東北大と九州大などの研究チームは 16 日、新型コロナウイルスの治療薬として使われる「レムデシビル」が引き起こす心機能への副作用について、その仕組みを解明したと発表した。成果は、副作用の抑制につながると期待される。論文は同日までに、国際科学誌コミュニケーションズ・バイオロジーに掲載された。

5/17　住友ファーマ、Exscientia（本社：英オックスフォード）の AI 生まれの精神疾患薬の Ph1 試験を開始

5/17　Sony の高分子技術で紐づく子分付き抗体による癌治療をアステラスが開発

5/18　Teva と AbbVie に続いて AstraZeneca も米国製薬協を脱退

https://www.statnews.com/2023/05/16/astrazeneca-leaves-phrma/

5/18　武田薬品が KSQ（本社：マサチューセッツ州レキシントン市）との癌治療標的探しの提携を拡大

5/18　理研、「10 年ルール」で 97 人雇い止め　チームリーダーの研究者も

5/19　新種の草食恐竜の化石、世界最大級と発表 アルゼンチン古生物学者

アルゼンチンで発見された新種の草食恐竜、チュカロサウルス・ディリピエンダの化石から、この恐竜が世界最大級だったと判明した。

5/19　『iPS 細胞使った心筋シート移植計画』完了　大阪大学大学院・澤特任教授らのグループ

5/23　「梅毒」5,000 人超、最多の昨年より 1 か月早いペース…「先天梅毒」の増加懸念

5/23　サル痘、国内新規感染続く　WHO は「緊急事態」終了　専門家「今後も警戒を」

5/24　山口大教授、論文 6 本で研究不正の疑い　実験の画像データ加工か

山口大大学院医学系研究科の男性教授が 2001～22 年に共同研究者と連名で執筆した論文 6 本に、実験結果の画像データを加工したような痕跡が見つかり、捏造（ねつぞう）や改ざんなどの研究不正の疑いがあることが大学関係者への取材で判明した。山口大は調査会を設置して調べている。研究不正の疑いがある 6 本は、欧州分子生物学機構や米国微生物学会などが出版する分子生物学分野の国際学術誌に掲載された。いずれもこの男性教授が論文の責任著者を務めた。生物の持つたんぱく質が別のたんぱく質に及ぼす影響を調べ、腫瘍の形成や細胞の増殖メカニズムなどに関する研究成果をまとめている。
6 本の論文で男性教授らは、ヒトのがん細胞やマウスの皮膚細胞などからたんぱく質を抽出する実験

をした。抽出したたんぱく質を「電気泳動」という手法で分析し、特定のたんぱく質が作られているか調べた。 特定のたんぱく質が存在すれば、撮影した画像から確認できる。ところが関係者によると、画像データを不自然に切り張りしたり、一部消去したりしたような痕跡が見つかったという。うち 1 本では、画像の切り張りなど不正と疑われる行為が最多の 33 カ所あった。
画像の操作・改変はデータの捏造や改ざんに該当する場合があり、山口大の調査会が不正と認定すれば、国の研究不正に関するガイドラインで研究費返還などの罰則対象となる。画像の切り張りは 14 年に「STAP 細胞」論文でも問題となった。

5/24　「パンデミックは終わっていない」WHO 緊急委員が再拡大へ警戒訴え

5/24　歯ぎしりと食物繊維不足に関係か　岡山大学などが研究結果を発表

睡眠中の歯ぎしりは、食物繊維不足が原因かも――。岡山大学とノートルダム清心女子大学の研究グループは 24 日、野菜や根菜類、バナナなどに多く含まれる食物繊維の摂取量が、歯ぎしりの発生と関係する可能性があると発表した。歯ぎしりは歯が欠け、歯周病が進みやすくなるとされるが、新たな対処法を提案できる可能性があるという。

5/25　RNA 薬開発会社 ReNAgade Therapeutics（本社：マサチューセッツ州ケンブリッジ市）が 3 億ドル調達して発足

ReNAgade Therapeutics Launches with over $300 Million in Series A Financing To Unlock the Limitless Potential of RNA Medicine | Business Wire

5/25　Braeburn（本社：ペンシルバニア州）のオピオイド依存症治療皮下注射剤を FDA が承認

FDA Approves New Buprenorphine Treatment Option for Opioid Use Disorder (prnewswire.com)

5/26　新種の鉱物「北海道石」発見　紫外線で黄緑の蛍光

5/26　大塚製薬が手放した Akebia（本社：マサチューセッツ州ケンブリッジ市）の貧血薬権利をドイツの Medice が手に入れる

Akebia Therapeutics Enters into License Agreement with Medice Arzneimittel Pütter GmbH&Co.KG for the Commercialization of Vafseo® for the Treatment of Anemia associated with CKD in Europe and Australia | Akebia Therapeutics

5/27　武田薬品が中国以外での権利を有する大腸癌薬 fruquintinib を米国が優先審査中

企業関連ニュース/他のトップページに戻る

今月の研究関連ニュース/他

1. ストレスは雌マウスのアルツハイマー病リスクを増加させるが、雄マウスでは増加させない
   メスのマウスではストレスに反応してアルツハイマー病のタンパク質が急激に上昇

2. 空腹感自体がハエの老化を遅らせる可能性

3. 肥満において食欲を促進する脳細胞を特定 -マウス実験

4. 癌細胞は糖分がないとき、違う燃料を消費する

5. 高糖分の食事が炎症性腸疾患を悪化させる理由 -マウス実験

6. 慢性治療抵抗性創傷の細菌バリアを突破 -マウス実験

7. 中年期を通じてランニングを続けると、「古い」成人期のニューロンが「配線された」ままになる
   「走るマウス」研究により、運動が老化時の記憶機能の維持にどのように役立つかが明らかに

8. 体内時計が内外のリズムと同期する性質を簡便に評価する手法

9. 40Hz の振動がアルツハイマー病マウスモデルの症状を軽減

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ソース：ワシントン大学医学部
概要：

女性はアルツハイマー病と診断される可能性が男性の約 2 倍である。米国では、女性は男性より 5～6 歳長生きしており、高齢はアルツハイマー病の最大の危険因子のため、その理由の一部は年齢によるものと考えられる。しかし、アルツハイマー病の研究者らは、女性がこの致命的な神経変性疾患のリスクが高い他の理由を探し続けている。
セントルイスのワシントン大学医学部の研究者らによる研究では、ストレスが脳に与える影響は、少なくともマウスでは性別によって異なることが示された。ストレスの多い状況では、女性の脳ではアルツハイマー病のタンパク質であるアミロイドベータのレベルが急激に上昇するが、男性では上昇しない。さらに、研究者らは、雄マウスではなく雌マウスの脳細胞で活性化する分子経路を特定し、それがストレスに対する多様な反応の原因であることを示した。
ストレスがアルツハイマー病の性差を引き起こす唯一の要因であるとは言えない、すなわち、ホルモン、ライフスタイル、その他の疾患など、男性と女性の間には他にも多くの違いがあり、それらが何らかの形で寄与していることは間違いないものの、ストレスがこの性差の一側面を引き起こしている可能性が非常に高い、としている。
5 月 2 日に「Brain」誌に掲載されたこの研究結果は、性別が健康と病気に重要であるという証拠としてさらに強化するものとなった。アルツハイマー病だけでなく、癌、心臓病、関節炎に至るまで、男性と女性の違いが、慢性疾患の予防や治療に対する反応に潜在的に影響を与える可能性がある、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞Stress increases Alzheimer's risk in female mice but not males: Alzheimer's proteins rise sharply in response to stress in female mice -- ScienceDaily

Stress increases Alzheimer's risk in female mice but not males

Alzheimer's proteins rise sharply in response to stress in female mice

Date:

May 2, 2023

Source:

Washington University School of Medicine

Summary:

Stress causes the levels of Alzheimer's proteins to rise in females' brains but not males' brains, according to a new study. This difference may contribute to women's greater risk of developing Alzheimer's disease.

FULL STORY

Women are about twice as likely as men to be diagnosed with Alzheimer's disease. Some of that is age; in the U.S., women outlive men by five to six years, and advanced age is the strongest risk factor for Alzheimer's. But there's more to it than that, so Alzheimer's researchers continue to look for other reasons why women have an elevated risk of the deadly neurodegenerative disease.

Stress may be one such reason. A study by researchers at Washington University School of Medicine in St. Louis shows that the effect stress has on the brain differs by sex, at least in mice. In stressful situations, levels of the Alzheimer's protein amyloid beta rises sharply in the brains of females but not males. In addition, the researchers identified a molecular pathway that is active in brain cells from female mice but not male mice, and showed that it accounts for the divergent responses to stress.

The findings, published May 2 in *Brain*, add to a growing collection of evidence that sex matters in health and disease. From cancer to heart disease to arthritis, scientists have found differences between males and females that could potentially affect how men and women respond to efforts to prevent or treat chronic diseases.

"How women respond to stress versus how men respond to stress is an important area of research that has implications for not just Alzheimer's disease but other conditions, too," said co-corresponding author Carla M. Yuede, PhD, an associate professor of psychiatry. "In recent years, the National Institutes of Health (NIH) has prioritized understanding sex differences in medicine. Stress is one area in which you can clearly see a difference between males and females. This study shows that reducing stress may be more beneficial for women than men, in terms of lowering the risk of Alzheimer's disease."

Stress falls into the category of socioeconomic risk factors, along with factors such as depression and social isolation, that together account for an estimated 8% of the risk of developing Alzheimer's. That risk calculation, however, doesn't take gender into account. Women consistently report higher levels of stress than men, and stress affects women's bodies differently than men's in many ways, such as cardiovascular health, immune responses and other issues.

Corresponding author John Cirrito, PhD, an associate professor of neurology; Yuede; and first author Hannah Edwards, a graduate student in Cirrito's lab, reasoned that stress also may affect women's brains differently than men's, and these differences may help explain the sex imbalance in Alzheimer's disease.

To find out, they measured levels of amyloid beta -- a key Alzheimer's protein -- in the brains of mice every hour for 22 hours, beginning eight hours before the mice experienced stress. The

experience was equally stressful for male and female mice, as measured by the levels of stress hormones in their blood. But the responses in their brains were not the same.

In female mice, amyloid beta levels rose significantly within the first two hours and stayed elevated through the end of the monitoring period. In male mice, brain amyloid levels did not change overall, although about 20% of them did show a delayed and weak rise in amyloid levels.

Further experiments revealed that the difference comes down to a cellular stress response pathway in brain cells. Stress causes the release of a hormone known as corticotropin releasing factor. Neurons from female rodents take up the stress hormone, triggering a cascade of events that results in increasing levels of amyloid beta in the brain. In contrast, neurons from male rodents lack the ability to take up the stress hormone. It is not known whether there are similar sex differences in how human neurons take up stress hormones.

"There's a fundamental biological difference between males and females in how they respond to stress at the cellular level, in both mice and people," Cirrito said. "We don't think that stress is the sole factor driving the sex difference in Alzheimer's disease. There are many other differences between men and women -- in hormones, lifestyle, other diseases they have -- that undoubtedly contribute in some way. But that stress is driving one aspect of this sex difference I think is very likely."

Story Source:

Materials provided by **Washington University School of Medicine**. Original written by Tamara Bhandari. *Note: Content may be edited for style and length.*

Journal Reference:

1. Hannah M Edwards, Clare E Wallace, Woodrow D Gardiner, Brookelyn M Doherty, Ryan T Harrigan, Kayla M Yuede, Carla M Yuede, John R Cirrito. **Sex-dependent effects of acute stress on amyloid-β in male and female mice**. *Brain*, 2023; DOI: 10.1093/brain/awad052

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2. 空腹感自体がハエの老化を遅らせる可能性

日付:2023 年 5 月 11 日
ソース:ミシガン大学
概要:

低炭水化物から断続的な断食、手術からオゼンピックまで、人々は体重を減らすために、一見終わりのない一連の食事療法、処置、薬に頼っている。食物の量を制限すると、人間を含む幅広い動物の健康的な老化を促進できることは長い間理解されてきたが、ミシガン大学の新しい研究では、空腹感自体が老化を遅らせるのに十分である可能性があることが明らかになった。
研究チームは、食物を求める衝動を促す脳の変化が長寿の背後にある可能性があるかどうかを調査するために、いくつかの方法でハエに空腹感を引き起こした。
1 つ目は、テスト用スナック食品に含まれる分岐鎖アミノ酸 (BCAA) の量を変え、その後、ハエにイーストまたは砂糖の入ったビュッフェを自由に食べさせた。低 BCAA スナックを与えたハエは、高 BCAA スナックを与えたハエよりもビュッフェ内の砂糖よりも多くのイーストを消費した。 このように砂糖よりもイーストを好むのは、ニーズに基づく飢餓の指標の 1 つである。研究者らは、この行動は低 BCAA スナックのカロリー量によるものではないと指摘しており、実際、これらのハエはより多くの餌とより多くの総カロリーを消費した。ハエが低 BCAA 食を生涯にわたって食べた場合、高 BCAA 食を与えたハエよりも著しく長生きした。
食物組成とは別に空腹を調べるために、彼らは、光遺伝学と呼ばれる技術を使用して、赤色光への曝露を利用してハエの空腹衝動に関連するニューロンを活性化するという独自の技術を使用した。これらのハエは、光刺激を受けなかったハエに比べて 2 倍の食物を消費した。また、赤色光で活性化したハエは、対照として使用したハエよりも著しく長生きした。
研究者らは、ハエにある種の飽くなき飢えを生み出し、それによってハエはより長く生きられるようになった、としている。彼らは次に、ハエと人間の両方に存在する快楽のために食べる衝動が寿命とどのように関連しているのかを調べることを計画している。

研究関連ニュース/他のトップページに戻る

＜英文＞The feeling of hunger itself may slow aging in flies -- ScienceDaily

The feeling of hunger itself may slow aging in flies

Date:

May 11, 2023

Source:

Michigan Medicine - University of Michigan

Summary:

While it has been long understood that limiting the amount of food eaten can promote healthy aging in a wide range of animals, including humans, a new study has revealed that the feeling of hunger itself may be enough to slow aging.

FULL STORY

From low-carb to intermittent fasting, surgery to Ozempic -- people turn to a seemingly never-ending array of diets, procedures and drugs to lose weight. While it has been long understood that limiting the amount of food eaten can promote healthy aging in a wide range of animals, including humans, a new study from University of Michigan has revealed that the feeling of hunger itself may be enough to slow aging.

Previous research has demonstrated that even the taste and smell of food can reverse the beneficial, life-extending effects of diet restriction, even without its consumption.

These intriguing findings drove first author Kristy Weaver, Ph.D., principal investigator Scott Pletcher, Ph.D., and their colleagues to examine whether changes in the brain that prompt the drive to seek food could be behind longer life.

"We've sort of divorced [the life extending effects of diet restriction] from all of the nutritional manipulations of the diet that researchers had worked on for many years to say they're not required," said Pletcher. "The perception of not enough food is sufficient."

To do this, they induced hunger in flies in several ways. The first was to alter the amount of branched-chain amino acids, or BCAAs, in a test snack food and later allow the flies to freely feed on a buffet of yeast or sugar food. Flies fed the low-BCAA snack consumed more yeast than sugar in the buffet than did the flies fed the high-BCAA snack. This kind of preference for yeast over sugar is one indicator of need-based hunger.

The researchers noted that this behavior wasn't due to the calorie content of the low-BCAA snack; in fact, these flies consumed more food and more total calories. When flies ate a low-BCAA diet for life, they also lived significantly longer than flies fed high-BCAA diets.

To look at hunger apart from dietary composition, they used a unique technique, activating neurons associated with the hunger drive in flies using exposure to red light, using a technique called optogenetics. These flies consumed twice as much food than did flies who were not exposed to the light stimulus. The red-light activated flies also lived significantly longer than flies used as a control.

"We think we've created a type of insatiable hunger in flies," said Weaver. "And by doing so, the flies lived longer."

What's more, the team was able to map the molecular mechanics of hunger to changes in the epigenome of the neurons involved -- and to identify that neurons responded to the presence or absence of a specific amino acid in the diet. These changes can affect how much of specific genes are expressed in the brains of flies and, consequently, their feeding behavior and aging.

The authors note that caution should be used before applying the findings to people, but "there's every reason to expect that the mechanisms discovered are likely to modulate hunger drives in other species."

They next plan to examine how the drive to eat for pleasure, present in both flies and people, may also be linked to lifespan.

Story Source:

Materials provided by **Michigan Medicine - University of Michigan**. Original written by Kelly Malcom. *Note: Content may be edited for style and length.*

Journal Reference:

1. K. J. Weaver, R. A. Holt, E. Henry, Y. Lyu, S. D. Pletcher. **Effects of hunger on neuronal histone modifications slow aging in Drosophila**. *Science*, 2023; 380 (6645): 625 DOI: 10.1126/science.ade1662

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3. 肥満において食欲を促進する脳細胞を特定 –マウス実験

日付：2023 年 5 月 13 日
ソース：ガーバン医学研究所
概要：

ガーバン医学研究所の研究チームは、肥満による過剰な脂肪の蓄積など、体内のエネルギー過剰が長期間続いた時に食欲を増進させる脳細胞群を発見した。研究者らは、これらの細胞が食欲を刺激する分子 NPY を生成するだけでなく、実際にその分子に対する脳の感受性を高め、食欲をさらに高めることを発見した。
肥満は重大な公衆衛生上の問題であり、成人 10 人に 1 人以上が罹患し、糖尿病や心臓病などの他の慢性疾患を発症するリスクを高める病気である。肥満（体内の脂肪組織の過剰な蓄積）の進行には多くの要因が影響を及ぼすが、食事パターンと身体活動レベルが主な要因である。
我々の脳には、体内にどれだけのエネルギーが蓄えられているかを感知し、それに応じて食欲を調整する複雑なメカニズムがある。これを行う方法の 1 つは、空腹などのストレスに反応して脳が自然に生成して摂食を刺激する分子 NPY によるものであるが、摂取エネルギーが消費エネルギーを下回ると、脳はより高いレベルの NPY を生成する。摂取エネルギーが消費エネルギーを上回ると、NPY レベルが低下し、空腹感が減る。しかし、エネルギー余剰が長期間続くと、 肥満における過剰な体脂肪として、NPY は低レベルでも食欲を促進し続ける。研究者らはその理由を理解したいと考えた。
研究者らは、マウスの肥満モデルで、NPY を産生するニューロンと呼ばれる脳内の細胞を調査したところ、驚くべきことに、そのうちの 15%が異なっており、それらは肥満中に NPY の産生を停止させないということを発見した。研究者らは、今回の発見により、抗肥満薬開発への新たなアプローチとして、さらに増感された NPY 受容体をブロックする可能性が開かれたと述べている。
この研究は、「Cell Metabolism」誌に掲載されている。

研究関連ニュース/他のトップページに戻る

＜英文＞Researchers pinpoint brain cells that drive appetite in obesity -- ScienceDaily

Researchers pinpoint brain cells that drive appetite in obesity

Date:

May 17, 2023

Source:

Garvan Institute of Medical Research

Summary:

A group of brain cells discovered by researchers reveals a potential new approach to anti-obesity treatment.

FULL STORY

A team at the Garvan Institute of Medical Research has discovered a group of brain cells that boosts appetite when there is a prolonged surplus of energy in the body, such as excess fat accumulation in obesity.

The researchers discovered that these cells not only produced the appetite-stimulating molecule NPY, but they in fact made the brain more sensitive to the molecule, boosting appetite even more.

"These cells kickstart changes in the brain that make it more sensitive to even low levels of NPY when there is a surplus of energy in the body in the form of excess fat -- driving appetite during obesity," explains Professor Herbert Herzog, senior author of the study and Visiting Scientist at Garvan.

"Our study addresses a long-standing question about how appetite is controlled in obesity and has the potential to take the development of therapy into a new direction."

The research was published in the journal *Cell Metabolism*.

The discovery of a vicious cycle

Obesity is a major public health issue and a disease that affects more than one in 10 adults and increases a person's risk of developing other chronic conditions, such as diabetes or heart disease. While many factors can influence the development of obesity -- an excessive accumulation of fat tissue in the body -- eating patterns and physical activity levels are key contributors.

"Our brain has intricate mechanisms that sense how much energy is stored in our body and adjust our appetite accordingly. One way it does this is through the molecule NPY, which the brain produces naturally in response to stresses, such as hunger, to stimulate eating," says Professor Herzog.

"When the energy we consume falls short of the energy we spend, our brain produces higher levels of NPY. When our energy intake exceeds our expenditure, NPY levels drop and we feel less hungry. However, when there is a prolonged energy surplus, such as excess body fat in obesity, NPY continues to drive appetite even at low levels. We wanted to understand why."

In mouse models of obesity, the researchers investigated cells in the brain called neurons that produced NPY and discovered that surprisingly, 15% of them were different -- they did not shut down NPY production during obesity.

"We found that under obese conditions, appetite was mostly driven by NPY produced by this subset of neurons. These cells did not only produce NPY, but also sensitised other parts of the brain to produce additional receptors or 'docking stations' for the molecule -- supercharging appetite even further," says Professor Herzog.

"What we have uncovered is a vicious cycle that disrupts the body's ability to balance its energy input with energy storage and enhances obesity development."

Wired to resist weight loss

"Our brain is wired to resist energy deficiency or weight loss, as it sees this as a threat to our survival and kickstarts mechanisms that increase our appetite so that we seek out food. As we found now, this even occurs when we have excess energy stored in the body," Professor Herzog explains.

The researchers say their discovery opens the possibility of blocking the additional, more sensitised receptors for NPY as a new approach to developing anti-obesity medication.

"Our discovery helps us better understand the mechanisms in the brain that interfere with a balanced energy metabolism and how they may be targeted to improve health," says Professor Herzog.

Story Source:

Materials provided by **Garvan Institute of Medical Research**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Yue Qi, Nicola J. Lee, Chi Kin Ip, Ronaldo Enriquez, Ramon Tasan, Lei Zhang, Herbert Herzog. **Agrp-negative arcuate NPY neurons drive feeding under positive energy balance via altering leptin responsiveness in POMC neurons**. *Cell Metabolism*, 2023; DOI: 10.1016/j.cmet.2023.04.020

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4. 癌細胞は糖分がないとき、違う燃料を消費する

日付：2023 年 5 月 17 日
ソース：ミシガン大学
概要：

「Nature」誌に掲載されたこの研究結果は、癌細胞がグルコースにアクセスできない場合でも適応できることを示している。 研究者らはこれまでに、膵臓癌の燃料源となる他の栄養素を特定しているが、この研究によりウリジンがリストに追加された。
ウリジンは腫瘍微小環境に存在するが、その正確な供給源と、癌細胞がどのようにしてウリジンにアクセスするのかは依然として謎のままである。
血液へのアクセスが制限されたり、細胞間の激しい競争が原因で細胞に充分な栄養素がなくなるときは、癌細胞がなぜ、どこでウリジンに向かうのかを知る手がかりとなる可能性がある。研究チームは、この未知の制御プロセスと、膵臓癌によく見られる KRAS 遺伝子の癌促進変異を、癌細胞がウリジンの使用を制御する 2 つの方法として認識している。
この研究では、また、ウリジンが酵素ウリジンホスホリラーゼ-1（UPP1）によって代謝されることを示している。UPP1 の阻害はマウスの膵臓腫瘍の増殖に大きな影響を及ぼし、新しい治療選択肢の可能性として、ウリジンを阻害する薬剤を試験する重要性を示唆する研究結果だ、としている。

研究関連ニュース/他のトップページに戻る

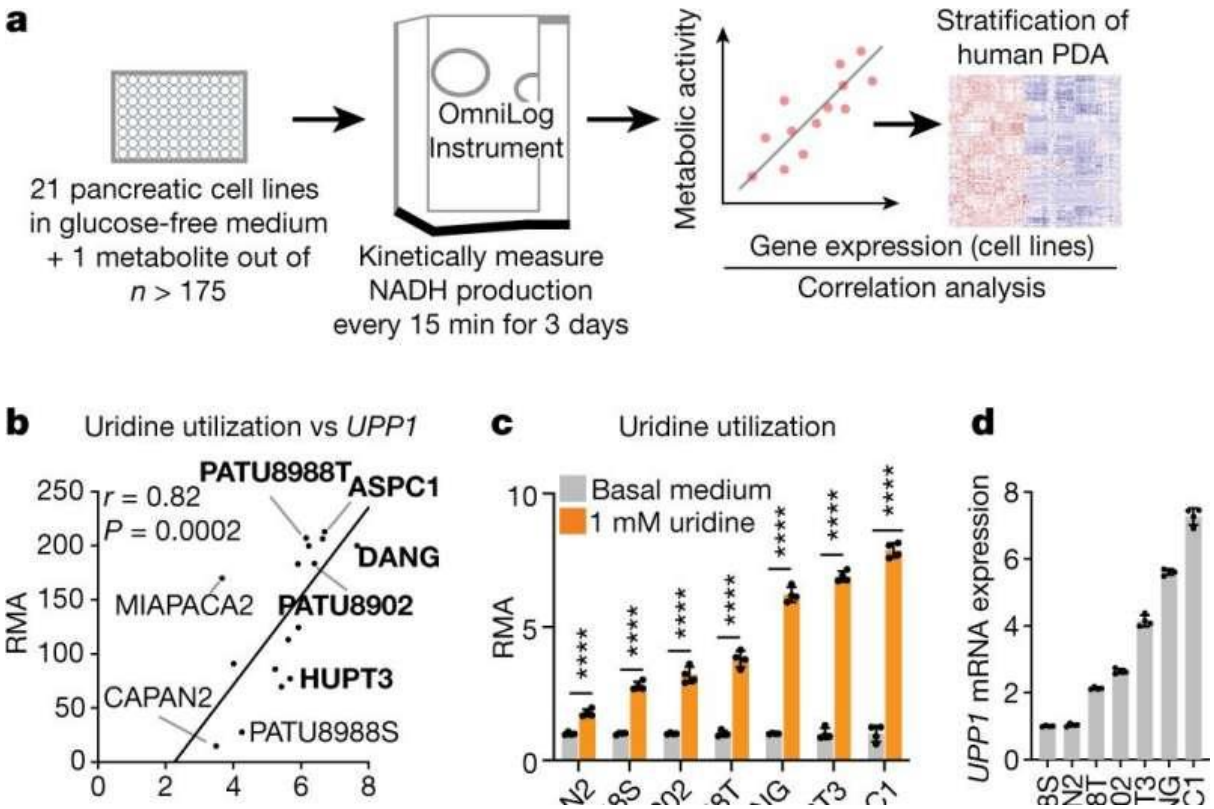
＜英文＞Study finds cancer cells use a new fuel in absence of sugar (medicalxpress.com)

MAY 17, 2023

Editors' notes

Study finds cancer cells use a new fuel in absence of sugar

by Anna Megdell, University of Michigan



Profiling of metabolite utilization in PDA cells identifies uridine. Credit: *Nature* (2023). DOI: 10.1038/s41586-023-06073-w

Researchers at the University of Michigan Rogel Cancer Center have discovered a new nutrient source that pancreatic cancer cells use to grow. The molecule, uridine, offers insight into both biochemical processes and possible therapeutic pathways.

The findings, published in *Nature*, show that cancer cells can adapt when they don't have access to glucose. Researchers have previously identified other nutrients that serve as fuel sources for pancreatic cancer; this study adds uridine to the catalog.

Pancreatic tumors have few functioning blood vessels and can't easily access nutrients that come from the bloodstream, like glucose. Costas Lyssiotis, Ph.D., Maisel Research Professor of Oncology and lead investigator of the study, explained that without the right nutrients, the cancer cells get hungry. "We know they still grow, obviously, but what are they using to grow?" he said. "These findings show that, under certain circumstances, uridine is one of those fuels."

Asked about the impact, Zeribe Nwosu, Ph.D., one of the co-first authors in the study, says "the ability of cancer to switch to alternative nutrients has fascinated me for a long time. Blocking such compensatory switches could lead us to new treatments and that's the door we hope this study will open."

Uridine is present in the tumor microenvironment, but its exact source, and how cancer cells access it, remains a mystery. "Part of the picture is it's in the bloodstream, but we don't know where it's coming from specifically," said Lyssiotis. "Likely, it's coming from multiple places, and so far we haven't been able to pin it to a single source."

Events that Lyssiotis refers to as "times of crisis"—when cells don't have enough nutrients, because of limited blood access and/or intense competition between cells—could be a clue as to why, and where, cells turn to uridine. "The cancer cells seem to be sensing the concentrations of glucose and uridine in the local environment to inform their adaptation," says Matt Ward, another co-first author. Lyssiotis' team recognize this unknown regulatory process, as well as a cancer-promoting mutation in the KRAS gene, which is common in pancreatic cancer, as two ways that cancer cells control their usage of uridine.

Lyssiotis and his team have been working on this research for nearly a decade alongside their collaborators in the Sadanandam lab at the Institute for Cancer Research in London. They used a technology that screens hundreds of different nutrients to see which ones support pancreatic cancer growth. Typically, researchers look at standard nutrients like sugar, protein and fat, but Lyssiotis's team took an unbiased approach.

"We used a large panel with over 20 pancreatic cell lines and around 200 different nutrients to assess different ways pancreatic cancer cells grow," he explained. "What do they actually metabolize? This method led us to discover uridine."

This method offers therapeutic insight, too. The findings showed that uridine is metabolized by the enzyme uridine phoshorylase-1, or UPP1. Blocking UPP1 had a major impact on the growth of pancreatic tumors in mice, findings that suggest the importance of testing drugs that block uridine as possible new treatment options.

"There's potential to better understand and treat pancreatic cancer with new drug targets and new therapeutic approaches," said Sadanandam, co-author on the study.

More research is needed to determine the best way to move this discovery to the clinic.

More information: Zeribe C. Nwosu et al, Uridine-derived ribose fuels glucose-restricted pancreatic cancer, *Nature* (2023). DOI: 10.1038/s41586-023-06073-w

Journal information: Nature

5. 高糖分の食事が炎症性腸疾患を悪化させる理由 −マウス実験

日付：2023 年 5 月 22 日
ソース：ピッツバーグ大学
概要：

ピッツバーグ大学の科学者らによる新たな研究によると、炎症性腸疾患（IBD）のマウスモデルにおいて、過剰な糖分が結腸の内壁を再生する細胞を妨げるという。
「Cellular and Molecular Gastroenterology and Hepatology」誌に発表されたこの研究結果は、なぜ甘い食べ物を制限すると IBD 患者の症状が緩和されるのかを解明するのに役立つ可能性がある。
研究者らは、マウスに標準食または高糖質食を与えることから始めた。次に、結腸に損傷を与える DSS と呼ばれる化学物質で動物を処理することで、IBD の症状を模倣した。
驚いたことに、高糖質食を与えたマウスはすべて 9 日以内に死亡、対照的に、標準食を与えた動物はすべて、14 日間の実験が終了するまで生存した。
IBD 症状のあるマウスにとって砂糖がなぜこれほど致死的になるのかを知るために、研究チームは動物の結腸を観察した。大腸としても知られる結腸は、陰窩と呼ばれる指のような突起に配置された上皮細胞の層で覆われていて、健康な結腸では、これらの細胞は各陰窩の底で分裂する幹細胞によって継続的に補充される。高糖食のマウスに DSS を与えたところ、その回路が崩壊した。さらに一部のマウスでは、上皮細胞の保護層が完全に失われ、結腸が血液と免疫細胞で満たされてしまった。
次に研究チームは、砂糖がマウスとヒトのコロノイド（実験用皿の中で培養できるケシの実サイズの小型腸）にどのような影響を与えるかをテストした。グルコース、サッカロース、またはフルクトースの濃度が増加すると、発達するコロノイドの数が減り、成長が遅くなった。これは、砂糖が細胞分裂を損なったことを示している。
彼らの研究は、高レベルの砂糖を摂取すると、炎症性腸疾患患者の結腸の修復に悪影響を及ぼす可能性があることを示している。

研究関連ニュース/他のトップページに戻る

＜英文＞Study may explain why high-sugar diets can wo | EurekAlert!

NEWS RELEASE 22-MAY-2023

Study may explain why high-sugar diets can worsen IBD

Peer-Reviewed Publication

UNIVERSITY OF PITTSBURGH

IMAGE: TIMOTHY HAND, PH.D., ASSOCIATE PROFESSOR OF PEDIATRICS AND IMMUNOLOGY AT THE UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE AND UPMC CHILDREN'S HOSPITAL OF PITTSBURGH. view more

CREDIT: UNIVERSITY OF PITTSBURGH

Excess sugar hampers cells that renew the colon's lining in a mouse model of inflammatory bowel disease (IBD), according to a new study by University of Pittsburgh scientists.

The findings, published in *Cellular and Molecular Gastroenterology and Hepatology*, could help get to the bottom of why limiting sugary foods can ease symptoms for patients with IBD.

"The prevalence of IBD is rising around the world, and it's rising the fastest in cultures with industrialized, urban lifestyles, which typically have diets high in sugar," said senior author Timothy Hand, Ph.D., associate professor of pediatrics and immunology at Pitt's School of Medicine and UPMC Children's Hospital of Pittsburgh. "Too much sugar isn't good for a variety of reasons, and our study adds to that evidence by showing how sugar may be

harmful to the gut. For patients with IBD, high-density sugar — found in things like soda and candy — might be something to stay away from."

Led by Ansen Burr, Ph.D., a student in Pitt's Medical Scientist Training Program, the researchers started by feeding mice either a standard or high-sugar diet. Then they mimicked symptoms of IBD by treating the animals with a chemical called DSS that causes damage to the colon.

To their shock, all the mice on the high-sugar diet died within nine days. In contrast, all the animals on the standard diet survived until the end of the 14-day experiment.

To learn what made sugar so deadly in mice with IBD symptoms, the team looked at the animals' colons. Also known as the large intestine, the colon is lined with a layer of epithelial cells that are arranged in finger-like projections called crypts. In a healthy colon, these cells are continually replenished by dividing stem cells at the bottom of each crypt.

"The colon epithelium is like a conveyor belt," said Hand, who is also director of Pitt's Gnotobiotic Animal Core Laboratory. "It takes five days for cells to travel through the circuit from the bottom to the top of the crypt, where they are shed into the colon and defecated out. You essentially make a whole new colon every five days."

When mice on the high-sugar diet were given DSS, that circuit collapsed, said Hand. In some of the animals, the protective layer of epithelial cells was completely lost, causing the colon to be full of blood and immune cells.

Unexpectedly, a high-sugar diet was similarly lethal in germ-free mice treated with DSS, showing that sugar affects the colon directly and is not dependent on the gut microbiome as the researchers had predicted.

Next, the team tested how sugar affected mouse and human colonoids, poppy seed-sized miniature intestines that can be grown in a lab dish. As concentrations of glucose, sucrose or fructose increased, fewer colonoids developed and they grew slower, evidence that sugar impaired cell division.

"We found that stem cells were dividing much more slowly in the presence of sugar — likely too slow to repair damage to the colon," said Hand. "The other strange thing we noticed was that the metabolism of the cells was different. These cells usually prefer to use fatty acids, but after being grown in high-sugar conditions, they seemed to get locked into using sugar."

In sugary conditions, the cells had vastly altered metabolic pathways, and they produced lower levels of ATP, the energy-providing molecule that drives cellular processes. The researchers suspect that this rewiring of cellular pathways inhibits the capacity of stem cells to divide, slowing renewal of the colon lining and accelerating gut damage in IBD.

According to Hand, these findings could help explain other research that has linked sweetened beverages, including sodas, soft drinks and juices, to negative outcomes in IBD patients.

“If you eat an apple or an orange, you’re eating a lot of sugar, but that sugar is tied up in the fruit’s cells, so it takes a long time to digest and open up those cells to get the sugar,” said Hand. “Whereas if you drink a soda, the sugar is available almost the second it hits your intestine, and it’s easy to drink a huge amount of sugar in a very short time. Our research suggests that consuming high levels of sugar could have negative outcomes for repairing the colon in patients with inflammatory bowel disease.”

Hand said that future research, done in in collaboration with coauthor Semir Beyaz, Ph.D., assistant professor at Cold Spring Harbor Laboratory, will focus on understanding how diet and immune response can affect IBD.

“I think that we need to investigate more deeply what diets are going to benefit patients who have intestinal damage, whether that be from IBD or from radiation therapy to treat colon cancer,” said Hand. “It’s about a nutraceutical approach to colon damage, or the idea of finding the right diet for a particular patient.”

Other authors on the study were Junyi Ji, B.Med., of Tsinghua University; Kadir Ozler, B.S., Onur Eskiocak, B.S., and Brian Yueh, B.S., of Cold Spring Harbor Laboratory; and Heather L. Mentrup, Ph.D., Rachel Cumberland, B.A., Ashley V. Menk, B.S., Natalie Rittenhouse, B.S., Chris W. Marshall, Ph.D., Pailin Chiaranunt, B.S., Xiaoyi Zhang, M.D., Ph.D., Lauren Mullinax, M.D., Abigail Overacre-Delgoffe, Ph.D., Vaughn S. Cooper, Ph.D., Amanda C. Poholek, Ph.D., Greg M. Delgoffe, Ph.D., and Kevin P. Mollen, M.D., all of Pitt or UPMC.

This work was supported by the Richard King Mellon Institute for Pediatric Research, the National Institutes of Health (T32AI089443-10), the Damon Runyon Cancer Research Foundation (2360-19), the Kenneth Rainin Foundation and the Cancer Center Support Grant (5P30CA045508).

JOURNAL

Cellular and Molecular Gastroenterology and Hepatology

DOI

10.1016/j.jcmgh.2023.05.001

METHOD OF RESEARCH

Experimental study

SUBJECT OF RESEARCH

Animals

ARTICLE TITLE

Excess dietary sugar alters colonocyte metabolism and impairs the proliferative response to damage

ARTICLE PUBLICATION DATE

10-May-2023

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6. 慢性治療抵抗性創傷の細菌バリアを突破 –マウス実験

日付:2023 年 5 月 22 日
ソース:ノースカロライナ大学ヘルスケア
概要:

ノースカロライナ大学の研究者らは、新しい戦略を使用して、糖尿病マウスの傷口における困難な MRSA 感染を 94%減らすことに成功した。数匹のマウスの傷を完全に消毒することができ、残りのマウスでは細菌の負担が大幅に減少した。この研究成果は「Cell Chemical Biology」誌に掲載されている。
慢性創傷とは、適切に治癒しない開いた潰瘍または組織の損傷である。この種の創傷は、黄色ブドウ球菌などの細菌感染のため、治療が難しいことで知られている。さらに、メチシリン耐性黄色ブドウ球菌(MRSA)などの抗生物質に非常に耐性のある細菌感染症は、入院患者における生命を脅かす感染症の主な原因の 1 つでもある。
黄色ブドウ球菌は、私たちの免疫システムやその他の脅威から身を守るために、自身の周りに滑らかでぬるぬるした力場、つまりバイオフィルムを作り出す。バイオフィルムの障壁は非常に厚いため、免疫細胞も抗生物質も有害な細菌を貫通して中和することができない。UNC 医学部の研究者らは、パルミトレイン酸、ゲンタマイシン、非侵襲的超音波を組み合わせた新しい方法を開発し、黄色ブドウ球菌に感染した慢性創傷への薬物送達を改善することに成功した。

研究関連ニュース/他のトップページに戻る

＜英文＞Breaking through bacterial barriers in chronic treatment-resistant wounds -- ScienceDaily

Breaking through bacterial barriers in chronic treatment-resistant wounds

Date:

May 22, 2023

Source:

University of North Carolina Health Care

Summary:

Using a new strategy, researchers were able to reduce the challenging MRSA infection in the wounds of diabetic mice by 94%. They were able to completely sterilize the wounds in several of the mice, and the rest had significantly reduced bacterial burden.

FULL STORY

Chronic wounds are open sores or injured tissue that fail to heal properly. These types of wounds are notoriously challenging to treat because of bacterial infections like *Staphylococcus aureus*, or *S. aureus*. Additionally, bacterial infections that are highly resistant to antibiotics, such as methicillin-resistant *S. aureus* (MRSA), are one of the main causes of life-threatening infections in hospital patients.

To defend itself from our immune system and other threats, *S. aureus* can band together, creating a slick, slimy forcefield -- or biofilm -- around itself. The biofilm barrier is so thick that neither immune cells nor antibiotics can penetrate through and neutralize the harmful bacteria.

Researchers at the UNC School of Medicine and the UNC-NC State Joint Department of Biomedical Engineering have developed a new method that combines palmitoleic acid, gentamicin, and non-invasive ultrasound to help improve drug delivery in chronic wounds that have been infected with *S. aureus*.

Using their new strategy, researchers were able to reduce the challenging MRSA infection in the wounds of diabetic mice by 94%. They were able to completely sterilize the wounds in several of the mice, and the rest had significantly reduced bacterial burden. Their results were published in *Cell Chemical Biology*.

"When bacteria are not completely cleared from chronic wounds, it puts the patient at high risk for the infection recurring or of developing a secondary infection," said senior author Sarah Rowe-Conlon, PhD, a research associate professor in the Department of Microbiology and Immunology. "This therapeutic strategy has the potential to improve outcomes and reduce relapse of chronic wound infections in patients. We are excited about the potential of translating this to the clinic, and that's what we're exploring right now."

Biofilms act as a physical barrier to many classes of antibiotics. Virginie Papadopoulou, PhD, a research assistant professor in the UNC-NCSU Joint Department of Biomedical Engineering, was curious to know if non-invasive cavitation-enhanced ultrasound could create enough agitation to form open spaces in the biofilm to facilitate drug-delivery.

Liquid droplets which can be activated by ultrasound, called phase change contrast agent (PCCA), are applied topically to the wound. An ultrasound transducer is focused on the wound and turned on, causing the liquid inside the droplets to expand and turn into microscopic gas-filled microbubbles, when then move rapidly.

The oscillation of these microbubbles agitates the biofilm, both mechanically disrupting it as well as increasing fluid flow. Ultimately, the combination of the biofilm disruption and the increased permeation of the drugs through the biofilm allowed the drugs to come in and kill the bacterial biofilm with very high efficiency.

"Microbubbles and phase change contrast agents act as local amplifiers of ultrasound energy, allowing us to precisely target wounds and areas of the body to achieve therapeutic outcomes not possible with standard ultrasound," said Dayton, the William R. Kenan Jr. Distinguished Professor and Department Chair of the UNC-NCSU Joint Department of Biomedical Engineering. "We hope to be able to use similar technologies to locally delivery chemotherapeutics to stubborn tumors or drive new genetic material into damaged cells as well."

When the bacterial cells are trapped inside the biofilm, they are left with little access to nutrients and oxygen. To conserve their resources and energy, they transition into a dormant or sleepy state. The bacteria, which are known as persister cells in this state, are extremely resistant to antibiotics.

Researchers chose gentamicin, a topical antibiotic typically ineffective against *S. aureus* due to widespread antibiotic resistance and poor activity against persister cells. The researchers also introduced a novel antibiotic adjuvant, palmitoleic acid, to their models.

Palmitoleic acid, an unsaturated fatty acid, is a natural product of the human body that has strong antibacterial properties. The fatty acid embeds itself into the membrane of bacterial cells, and the authors discovered that it facilitates the antibiotic's successful entry into *S. aureus* cells and is able to kill persister cells and reverse antibiotic resistance.

Overall, the team is enthusiastic about the new topical, non-invasive approach because it may give scientists and doctors more tools to combat antibiotic resistance and to lessen the serious adverse effects of taking oral antibiotics.

"Systemic antibiotics, such as oral or IV, work very well, but there's often a large risk associated with them such as toxicity, wiping out gut microflora and *C. difficile* infection," said Rowe-Conlon. "Using this system, we are able to make topical drugs work and they can be applied to the site of infection at very high concentrations, without the risks associated with systemic delivery."

Story Source:

Materials provided by **University of North Carolina Health Care**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Virginie Papadopoulou, Ashelyn E. Sidders, Kuan-Yi Lu, Amanda Z. Velez, Phillip G. Durham, Duyen T. Bui, Michelle Angeles-Solano, Paul A. Dayton, Sarah E. Rowe. **Overcoming biological barriers to improve treatment of a Staphylococcus aureus wound infection**. *Cell Chemical Biology*, 2023; 30 (5): 513 DOI: 10.1016/j.chembiol.2023.04.009

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7. 中年期を通じてランニングを続けると、「古い」成人期のニューロンが「配線された」ままになる

「走るマウス」研究により、運動が老化時の記憶機能の維持にどのように役立つかが明らかに

日付：2023 年 5 月 25 日
ソース：フロリダ アトランティック大学
概要：

老化にはしばしば認知機能の低下が伴う。影響を受ける脳の最初の構造には、学習と記憶に不可欠な領域である海馬と隣接する皮質がある。認知能力の欠陥は、海馬容積の減少と、海馬と嗅内皮質（周囲）との間のシナプス接続の劣化と関連している。
近年、身体活動が高齢者の構造的および機能的低下を遅らせたり、予防したりできることを示す証拠が増えており、今回のフロリダ アトランティック大学とメキシコ、メキシコシティの CINVESTAV による新しい研究は、運動の利点に関する新たな洞察を提供し、成人が生涯を通じて、特に中年期に体を動かし続ける動機となるものだ。
この研究で研究者らは、若い成体マウス時に生成された新しい海馬ニューロンのネットワーク上における長期ランニングの影響に焦点を当てた。これらの「走るマウス」は、中年期に、ランニングを続けたことで、成人時に生まれた古いニューロンの配線が維持され、それによって加齢に伴う記憶喪失や神経変性が予防または遅延される可能性があることを示している。
この研究結果は、「eNeuro」誌に掲載されている。

研究関連ニュース/他のトップページに戻る

＜英文＞Running throughout middle age keeps ‘old’ adu | EurekAlert!

NEWS RELEASE 25-MAY-2023

Running throughout middle age keeps ‘old’ adult-born neurons ‘wired’

‘Mice on the run:’ study reveals how exercise helps maintain memory function during aging

Peer-Reviewed Publication

FLORIDA ATLANTIC UNIVERSITY

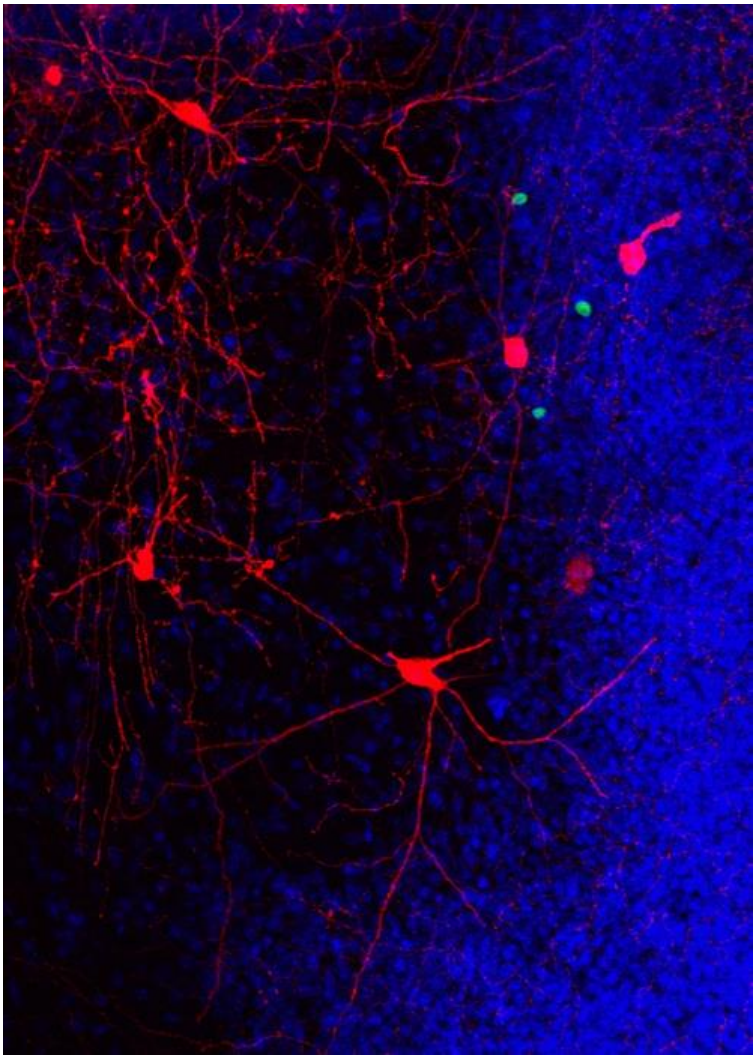

IMAGE: LONG-TERM RUNNING SUBSTANTIALLY MODIFIES THE NETWORK OF THE NEURONS GENERATED IN YOUNG ADULT MICE UPON MIDDLE-AGE. IMPORTANTLY, EXERCISE INCREASES INPUT FROM HIPPOCAMPAL INTERNEURONS (RED CELLS) ONTO 'OLD' ADULT-BORN NEURONS. THESE INTERNEURONS MAY PLAY A ROLE IN REDUCING AGING-RELATED HYPEREXCITABILITY OF THE HIPPOCAMPUS AND THEREBY BENEFIT MEMORY FUNCTION. view more

CREDIT: CARMEN VIVAR, PH.D.

Aging often is accompanied by cognitive decline. Among the first structures of the brain affected are the hippocampus and adjacent cortices, areas essential for learning and memory. Deficits in cognitive ability are associated with reduced hippocampal volume and degradation of synaptic connectivity between the hippocampus and the (peri)–entorhinal cortex.

Increasing evidence indicates that physical activity can delay or prevent these structural and functional reductions in older adults. A new study by Florida Atlantic University and CINVESTAV, Mexico City, Mexico, provides novel insight into the benefits of exercise, which should motivate adults to keep moving throughout their lifetime, especially during middle age.

For the study, researchers focused on the effects of long-term running on a network of new hippocampal neurons that were generated in young adult mice, at middle age. These "mice on the run" demonstrate that running throughout middle age keeps old adult-born neurons wired, which may prevent or delay aging-related memory loss and neurodegeneration.

Adult-born neurons are thought to contribute to hippocampus-dependent memory function and are believed to be temporarily important, during the so-called 'critical period' at about three to six weeks of cell age, when they can fleetingly display increased synaptic plasticity. However, these new neurons do remain present for many months, but it was unclear whether those born in early adulthood remain integrated into neural networks and whether their circuitry is modifiable by physical activity in middle age.

To address these questions, researchers used a unique rabies virus-based circuit tracing approach with a long-time interval between the initial labeling of new neurons and subsequent analysis of their neural circuitry in rodents. More than six months after tagging of the adult-born neurons with a fluorescent reporter vector, they identified and quantified the direct afferent inputs to these adult-born neurons within the hippocampus and (sub)cortical areas, when the mice were middle-aged.

Results of the study, published in the journal *eNeuro,* show long-term running wires 'old' new neurons, born during early adulthood, into a network that is relevant to the maintenance of episodic memory encoding during aging.

"Long-term exercise profoundly benefits the aging brain and may prevent aging-related memory function decline by increasing the survival and modifying the network of the adult-born neurons born during early adulthood, and thereby facilitating their participation in cognitive processes," said Henriette van Praag, Ph.D., corresponding author, an associate professor of biomedical science in FAU's Schmidt College of Medicine and a member of the FAU Stiles-Nicholson Brain Institute.

Findings from the study showed long-term running significantly increased the number of adult-born neurons and enhanced the recruitment of presynaptic (sub)-cortical cells to their network.

"Long-term running may enhance pattern separation ability, our ability to distinguish between highly similar events and stimuli, a behavior closely linked to adult neurogenesis, which is among the first to display deficits indicative of age-related memory decline," said Carmen Vivar, Ph.D., corresponding author, Department of Physiology, Biophysics and Neuroscience, Centro de Investigacion y de Estudios Avanzados del IPN in Mexico.

Aging-related memory function decline is associated with the degradation of synaptic inputs from the perirhinal and entorhinal cortex onto the hippocampus, brain areas that are essential for pattern separation, and contextual and spatial memory.

"We show that running also substantially increases the back-projection from the dorsal subiculum onto old adult-born granule cells," said van Praag. "This connectivity may provide navigation-associated information and mediate the long-term running-induced improvement in spatial memory function."

Results from the study show that running not only rescued perirhinal connectivity but also increased and altered the contribution of the entorhinal cortices to the network of old adult-born neurons.

"Our study provides insight as to how chronic exercise, beginning in young adulthood and continuing throughout middle age, helps maintain memory function during aging, emphasizing the relevance of including exercise in our daily lives," said Vivar.

Study co-authors are Ben Peterson, Ph.D., currently a postdoc at UC Davis; Alejandro Pinto, FAU's Schmidt College of Medicine and Stiles-Nicholson Brain Institute; and Emma Janke, a recent graduate of the University of Pennsylvania.

This research was supported in part by the FAU Stiles-Nicholson Brain Institute and the Jupiter Life Sciences Initiative (awarded to van Praag), and by the Fondo de Investigación Científica y Desarrollo Tecnológico del Cinvestav (Proyectos SEP-Cinvestav), (awarded to Vivar).

- FAU -

About the Charles E. Schmidt College of Medicine:

FAU's Charles E. Schmidt College of Medicine is one of approximately 156 accredited medical schools in the U.S. The college was launched in 2010, when the Florida Board of Governors made a landmark decision authorizing FAU to award the M.D. degree. After receiving approval from the Florida legislature and the governor, it became the 134th allopathic medical school in North America. With more than 70 full and part-time faculty and more than 1,300 affiliate faculty, the college matriculates 64 medical students each year and has been nationally recognized for its innovative curriculum. To further FAU's commitment to increase much needed medical residency positions in Palm Beach County and to ensure that the region will continue to have an adequate and well-trained physician workforce, the FAU Charles E. Schmidt College of Medicine Consortium for Graduate Medical Education (GME) was formed in fall 2011 with five leading hospitals in Palm Beach County. The Consortium currently has five Accreditation Council for Graduate Medical Education (ACGME) accredited residencies including internal medicine, surgery, emergency medicine, psychiatry, and neurology.

About Florida Atlantic University:

Florida Atlantic University, established in 1961, officially opened its doors in 1964 as the fifth public university in Florida. Today, the University serves more than 30,000 undergraduate and graduate students across six campuses located along the southeast Florida coast. In recent years, the

University has doubled its research expenditures and outpaced its peers in student achievement rates. Through the coexistence of access and excellence, FAU embodies an innovative model where traditional achievement gaps vanish. FAU is designated a Hispanic-serving institution, ranked as a top public university by U.S. News & World Report and a High Research Activity institution by the Carnegie Foundation for the Advancement of Teaching. For more information, visit www.fau.edu.

About Cinvestav:

The Center for Research and Advanced Studies (Cinvestav) was created by the Federal Government in 1961 as the first Mexican public institution offering only postgraduate research programs. Cinvestav is financed by the Mexican Ministry of Education. It´s mission is to perform cutting-edge basic and applied research, train high level human resources to provide the country with the necessary tools to offer scientific and technological solutions for our national problems. Cinvestav has presence in all Mexico with 10 campuses specialized in four different areas of research: Exact and Natural Sciences, Biological and Health Sciences, Technology and Sciences of engineering and Social Sciences and Humanities.

JOURNAL

eNeuro

DOI

10.1523/ENEURO.0084-23.2023

METHOD OF RESEARCH

Experimental study

SUBJECT OF RESEARCH

Cells

ARTICLE TITLE

Running throughout Middle-Age Keeps Old Adult-Born Neurons Wired

ARTICLE PUBLICATION DATE

15-May-2023

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8. 体内時計が内外のリズムと同期する性質を簡便に評価する手法

日付：2023 年 5 月 25 日
ソース：筑波大学
概要：https://www.tsukuba.ac.jp/journal/medicine-health/20230522140000.html

多くの生物は日周期で生じる光や温度の環境変化に適応するため、概日時計（体内時計）を備えています。概日時計は、環境や生体内のリズムに合わせて自身の時刻（位相）を調整するため、光や温度などの同期刺激に応じて位相を変化させる性質を持ち、この応答は刺激を受けた際の位相によっても変化します。これを一つのグラフにまとめたものは位相応答曲線（PRC）と呼ばれ、概日時計と内外の同期刺激との関係を明らかにする上で重要な役割を果たします。しかしながら、PRC を取得するためは、刺激を与えた時刻ごとの応答を逐一計測する必要があり、多くの時間とコストがかかることが課題でした。
本研究では、植物に見られる概日時計の脱同期状態（細胞それぞれの概日時計の時刻がばらばらになった状態）における刺激応答（特異点応答、SR）を用いた PRC 推定手法を哺乳類の概日時計に適用し、さまざまな刺激に対する概日時計の応答特性の評価を行いました。その結果、マウスやラットの培養細胞でも SR が観察されること、温度刺激や化学刺激などに対する概日時計の PRC を一度の計測から評価できることを示しました。さらに、マウスから得られた腎臓や肺などの組織切片を用いた計測により、組織によって同じ同期刺激でも応答の性質が異なることが分かりました。
本研究成果は、概日時計が環境や生体内の刺激に合わせて自身のリズムを調整するメカニズムの解明につながるとともに、時差ボケや概日リズム障害の治療薬の開発への応用も期待されます。

研究関連ニュース/他のトップページに戻る

＜英文＞Keeping time: Understanding the master clock in the brain: Researchers find a molecular pathway that controls sleep rhythms and homeostasis -- ScienceDaily

Keeping time: Understanding the master clock in the brain

Researchers find a molecular pathway that controls sleep rhythms and homeostasis

Date:

May 25, 2023

Source:

University of Tsukuba

Summary:

Researchers found that, in neurons that produced the neuropeptide NMS, the interaction between molecules SIK3 and HDAC4 has a critical role in sleep regulation through both the length of the circadian period and sleep homoeostasis. Given the similarities among different mammals, new information about how the circadian system works in mice could lead to new treatments for sleep and circadian rhythm disorders in humans.

FULL STORY

Most living creatures exhibit a circadian rhythm, an internal clock that repeats around every 24 hours. Now, researchers from Japan have found new details about the molecular processes that govern sleep/wake rhythms in mice.

In a recently published study, researchers from the University of Tsukuba have revealed that a key molecule involved in sleep homeostasis (called SIK3 or salt-inducible kinase 3) also plays a critical role in circadian behavior.

Animals are able to adapt to the 24-hour cycle of light and dark in terms of both behavior and physiology via changes in the suprachiasmatic nucleus (SCN), which is the brain's master clock that synchronizes the various rhythms in the body. However, the biological activities within the SCN that induce time-specific wakefulness have not been fully characterized; the research team aimed to address this.

"Most animals show a peak in activity at a specific point in the circadian cycle," explains lead author of the study Professor Masashi Yanagisawa. "Because the SCN has been found to regulate sleep and wakefulness at certain times of the day, we wanted to investigate the distinct neurons that control this process."

To do this, the research team genetically manipulated levels of SIK3 in specific neuron groups in the SCN of mice. Then, they examined sleep and circadian behaviors in the mice, such as when and for how long the mice exhibited activity with respect to the light-dark cycle.

"We found that SIK3 in the SCN can influence circadian cycle length and the timing of peak arousal activity, without changing the daily sleep amount," says Professor Yanagisawa.

The research team previously reported that SIK3 interacts with LKB1 (an upstream molecule of SIK3) and HDAC4 (an important target of SIK3) in glutamatergic neurons to regulate the amount and depth of sleep. Now, they have found that the SIK3-HDAC4 pathway modulates the length of the circadian period through NMS-producing neurons, and contributes to the sleep/wake rhythm.

The length of the behavioral period and the timing of peak activity are important components of the circadian rhythm. Given the similarities between the circadian systems of different mammals, new information about how this system works in mice could lead to new treatments for sleep and circadian rhythm disorders in humans.

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Journal Reference:

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9. 40Hz の振動がアルツハイマー病マウスモデルの症状を軽減

日付：2023 年 5 月 18 日
ソース：MIT ピコワー研究所
概要：

40Hz のガンマ周波数の脳リズムによる非侵襲的な感覚刺激がアルツハイマー病の病状と症状を軽減できるという証拠は、マウスとヒトを対象とした複数の研究グループによってすでに光と音で示されているが、今回マサチューセッツ工科大学の科学者らによる新しい研究では、アルツハイマー病マウスモデルを 1 日 1 時間、数週間にわたって 40Hz の振動にさらしたところ、未治療の対照マウスと比較して脳の健康状態と運動機能が改善されたことが示された。ガンマ周波数の触覚刺激が脳の活動に影響を与え、運動機能を改善できることを示した最初の研究ではないが、文字通りその振動刺激がアルツハイマー病の特徴であるタンパク質であるリン酸化タウのレベルを低下させ、ニューロンが死滅したりシナプス回路の接続を失うことを防ぎ、神経 DNA の損傷を軽減できることを初めて示した。この新しい研究では、2 種類のマウスモデルにおいて、全身 40Hz の触覚刺激が有意義な利益を生み出すかどうかをテストした。その 2 種類とは、アルツハイマー病の神経変性マウスモデルとして一般的に使用されるもので、アルツハイマー病のタウ病理を再現するタウ P301S マウスと、人間の病気で見られるシナプスの喪失と DNA 損傷を再現する CK-p25 マウスである。研究チームは、脳の 2 つの領域、すなわち触覚が処理される一次体性感覚皮質（SSp）と、脳が身体への運動命令を生成する一次運動野（MOp）に焦点を当てて分析を行った。振動刺激を生み出すために、研究者らは 40Hz の音を流すスピーカーの上にマウスケージを置き、ケージを振動させた。刺激を受けていない対照マウスは、すべてのマウスが同じ 40Hz の音を聞くように、同じ部屋に点在するケージの中に入れられたため、刺激されたマウスと対照マウスの間で測定された差は、触覚刺激の追加によって生じた実際の振動である、としている。

研究関連ニュース/他のトップページに戻る

＜英文＞40 Hz vibrations reduce Alzheimer's pathology | EurekAlert!

NEWS RELEASE 18-MAY-2023

40 Hz vibrations reduce Alzheimer's pathology, symptoms in mouse models

Peer-Reviewed Publication

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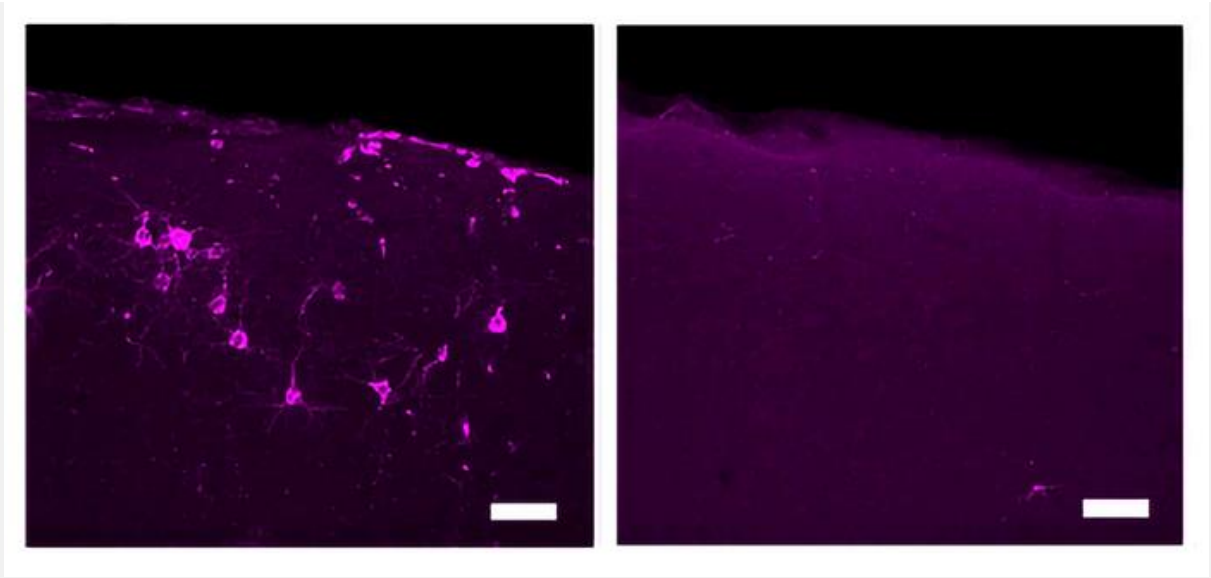

IMAGE: AN ENLARGED DETAIL FROM A FIGURE IN THE PAPER HIGHLIGHTS REDUCTIONS IN PHOSPHORYLATED TAU (MAGENTA) IN PRIMARY SOMATOSENSORY CORTICAL NEURONS IN TAU P301S MODEL MICE TREATED WITH 40 HZ TACTILE STIMULATION (RIGHT). AN IMAGE FROM AN UNTREATED CONTROL IS ON THE LEFT. view more

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Evidence that non-invasive sensory stimulation of 40 Hz gamma frequency brain rhythms can reduce Alzheimer's disease pathology and symptoms, already shown with light and sound by multiple research groups in mice and humans, now extends to tactile stimulation. A new study by MIT scientists shows that Alzheimer's model mice exposed to 40 Hz vibration an hour a day for several weeks showed improved brain health and motor function compared to untreated controls.

The MIT group is not the first to show that gamma frequency tactile stimulation can affect brain activity and improve motor function, but they are the first to show that the stimulation can also reduce levels of the hallmark Alzheimer's protein phosphorylated tau, keep neurons from dying or losing their synapse circuit connections, and reduce neural DNA damage.

"This work demonstrates a third sensory modality that we can use to increase gamma power in the brain," said Li-Huei Tsai, corresponding author of the study, director of The Picower Institute for Learning and Memory and the Aging Brain Initiative at MIT, and Picower Professor in the Department of Brain and Cognitive Sciences (BCS). "We are very excited to see that 40 Hz tactile stimulation benefits motor abilities, which has not been shown with the other modalities. It would be interesting to see if tactile stimulation can benefit human subjects with impairment in motor function."

Ho-Jun Suk, Nicole Buie, Guojie Xu and Arit Banerjee are lead authors of the study in *Frontiers in Aging Neuroscience* and Ed Boyden, Y. Eva Tan Professor of Neurotechnology at MIT, is a co-senior author of the paper. Boyden, an affiliate member of The Picwoer Institute, is also appointed in BCS as

well as the Departments of Bioengineering and Media Arts and Sciences, the McGovern Institute for Brain Research, and the K. Lisa Yang Cener for Bionics.

Feeling the vibe

In a series of papers starting in 2016, a collaboration led by Tsai's lab has demonstrated that light flickering and/or sound clicking at 40 Hz (a technology called GENUS for Gamma Entrainment Using Sensory stimuli), reduces levels of amyloid-beta and tau proteins, prevents neuron death and preserves synapses and even sustains learning and memory in a variety of Alzheimer's disease mouse models. Most recently in pilot clinical studies the team showed that 40 Hz light and sound stimulation was safe, successfully increased brain activity and connectivity and appeared to produce significant clinical benefits in a small cohort of human volunteers with early-stage Alzheimer's disease. Other groups have replicated and corroborated health benefits of 40 Hz sensory stimulation and an MIT spin-off company, Cognito Therapeutics, has launched stage III clinical trials of light and sound stimulation as an Alzheimer's treatment.

The new study tested whether whole-body 40 Hz tactile stimulation produced meaningful benefits in two commonly used mouse models of Alzheimer's neurodegeneration, the Tau P301S mouse, which recapitulates the disease's tau pathology, and the CK-p25 mouse, which recapitulates the synapse loss and DNA damage seen in human disease. The team focused its analyses in two areas of the brain: the primary somatosensory cortex (SSp), where tactile sensations are processed, and the primary motor cortex (MOp), where the brain produces movement commands for the body.

To produce the vibration stimulation, the researchers placed mouse cages over speakers playing 40 Hz sound, which vibrated the cages. Non-stimulated control mice were in cages interspersed in the same room so that all the mice heard the same 40 Hz sound. The differences measured between the stimulated and control mice were therefore made by the addition of tactile stimulation.

First the researchers confirmed that 40 Hz vibration made a difference in neural activity in the brains of healthy (i.e. non-Alzheimer's) mice. As measured by expression of c-fos protein, activity increased two-fold in the SSp and more than 3-fold in the MOp, a statistically significant increase in the latter case.

Once the researchers knew that 40 Hz tactile stimulation could increase neural activity, they assessed the impact on disease in the two mouse models. To ensure both sexes were represented, the team used male P301S mice and female CK-p25 mice.

P301S mice stimulated for three weeks showed significant preservation of neurons compared to unstimulated controls in both brain regions. Stimulated mice also showed significant reductions in tau in the SSp by two measures, and exhibited similar trends in the MOp.

CK-p25 mice received six weeks of vibration stimulation. These mice showed higher levels of synaptic protein markers in both brain regions compared to unvibrated control mice. They also showed reduced levels of DNA damage.

Finally the team assessed the motor abilities of mice exposed to the vibration vs. not exposed. They found that both mouse models were able to stay on a rotating rod significantly longer. P301S mice also hung on to a wire mesh for significantly longer than control mice while CK-p25 mice showed a positive, though non-significant trend.

"The current study, along with our previous studies using visual or auditory GENUS demonstrates the possibility of using non-invasive sensory stimulation as a novel therapeutic strategy for ameliorating pathology and improving behavioral performance in neurodegenerative diseases," the authors concluded.

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COI STATEMENT

Li-Huei Tsai and Ed Boyden are co-founders of Cognito Therapeutics, a company that has advanced 40Hz non-invasive sensory stimulation to phase III clinical trials.
