Bioinformatic search can verify serotonin as a neuromodulator. The unknown has been an explicit and verifiable explanation for the cellular mechanism of neuromodulation; i.e. until MCFIP used its quantum computational biology model to compile the findings outlined in the thread of documents affixed to this article.

https://medicalxpress.com/news/2019-06-debate-serotonin-role.html

JUNE 24, 2019

Settling the debate on serotonin's role in sleep

by California Institute of Technology

Serotonin is a multipurpose molecule found throughout the brain, playing a role in memory, cognition, and feelings of happiness and other emotions. In particular, researchers have long debated serotonin's role in sleep: Does serotonin promote sleep, or its opposite, wakefulness?

Now, Caltech scientists have found that serotonin is necessary for sleep in zebrafish and mouse models.

A paper describing the research appears online on June 24 in the journal *Neuron*. The work is a collaboration between the Caltech laboratories of David Prober, professor of biology and affiliated faculty member of the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech; and Viviana Gradinaru (BS '05), professor of neuroscience and biological engineering, Heritage Medical Research Institute Investigator, and director of the Chen Institute's Center for Molecular and Cellular Neuroscience.

Previous studies on serotonin and sleep have yielded conflicting results. Some research showed that serotonin promotes sleep, but other work showed that serotonin-producing neurons were most active and releasing the chemical during wakefulness.

In order to settle this debate, the Caltech team focused on a region called the raphe nuclei, which has the brain's main population of serotonin-producing (or serotonergic) neurons. The raphe are evolutionarily ancient structures found in the brain stem of a wide range of organisms from fish to humans, and they are responsible for both manufacturing and sending out serotonin to other brain regions.

Led by senior postdoctoral scholar Grigorios Oikonomou of the Prober lab, the research began using zebrafish, tiny transparent fish that are widely used as a model to study

sleep. Like humans, zebrafish larvae are diurnal—meaning that their sleep occurs mostly at night.

First, the researchers genetically mutated zebrafish so that their raphe did not produce serotonin. These mutant fish, the team found, slept about half as much as normal fish. In another experiment, the researchers removed the raphe altogether, and these fish also slept much less than usual.

"This suggests that serotonin produced by the raphe is required for the fish to get normal amounts of sleep," says Oikonomou.

In a third set of experiments, zebrafish were genetically modified so that their raphe could be activated by light. Shining a light on these fish put them to sleep, implying that activation of the raphe induces sleep. This effect requires serotonin, because activating the raphe in fish that do not synthesize serotonin had no effect on sleep.

The team from the Prober laboratory then collaborated with scientists in the Gradinaru laboratory to continue the serotonin studies in mice. Led by graduate student Michael Altermatt, the team examined serotonergic neurons in the mouse raphe and confirmed that they are indeed mostly active while the animals are awake and less active during sleep, in agreement with previous studies.

As Prober's lab did in zebrafish, the Gradinaru lab's team genetically removed the serotonergic neurons in the mouse raphe and found that the mice slept less than usual. Stimulating these neurons with light also put the mice to sleep but only when the light was administered at frequencies that are consistent with the naturally occurring baseline activity pattern of these neurons during wakefulness.

"There's an obvious paradox here: stimulating the neurons causes the animals to sleep, and yet the neurons are normally active during the day," says Altermatt.

Oikonomou explains: "There are two main factors that control sleep. One is the circadian clock—when it is light during the day, the body is awake, and when it gets dark, the body knows to sleep. The other factor is called homeostatic sleep pressure. When you wake up in the morning, you have just gotten rest, and so you're energetic. As the day goes on, you get tired and sleepy, so there is a building of pressure to sleep. If you don't sleep that night, your sleep pressure is even higher, and you are even more tired the next day even though it's light outside, and your circadian clock dictates that you should be awake."

"The theory is that, in order to sleep, you need to have high sleep pressure and the circadian clock needs to be aligned with the time of day—nighttime for diurnal creatures like us and daytime for nocturnal animals."

The researchers theorize that the firing of neurons in the raphe and their release of serotonin is a way for the brain to build up sleep pressure. Indeed, they found that

zebrafish lacking serotonin as well as mice with ablated raphe show reduced sleep pressure.

While the studies were in animal models, the raphe region and its production of serotonin are similar in human brains. The research can contribute to explanations of some sleep-related side effects of common antidepressant drugs that increase serotonin levels in the brain.

The paper is titled "The Serotonergic Raphe Promote Sleep in Zebrafish and Mice."

Neuromodulation Overview

Acetylcholine, dopamine and serotonin are known to be neuromodulators. The findings for CBD as a biosimilar for serotonin in BDNF are outlined in the document affixed to this article.

Neuropeptide modeling has identified, with near certainty, that dopamine is the neuromodulator for the catecholamines in NPY, serotonin is the neuromodulator for BDNF in PPY and acetylcholine is the neuromodulator PPY that regulates the interactions between NPY and PPY.

Summary

The role of neuromodulation is explained in the CBD document affixed to this article.

https://medicalxpress.com/news/2019-06-commonly-drugs-dementia.html

JUNE 24, 2019

Commonly prescribed drugs could increase the risk of dementia, says a new study

by University of Nottingham

The study, carried out by experts from the University of Nottingham and funded by the NIHR School for Primary Care Research, found that there was nearly a 50% increased

risk of dementia among patients aged 55 and over who had used strong anticholinergic medication daily for three years or more.

Anticholinergic drugs help to contract and relax muscles. They work by blocking acetylcholine, a chemical that transmits messages in the nervous system.

Doctors prescribe the drugs to treat a variety of conditions, including chronic obstructive pulmonary disease, bladder conditions, allergies, gastrointestinal disorders and symptoms of Parkinson's disease.

These medicines can have short-term side effects, including confusion and memory loss, but it is less certain whether long-term use increases the risk of dementia.

The research, published in the *JAMA Internal Medicine* journal and led by Professor Carol Coupland from the University's Division of Primary Care, looked at the medical records of 58,769 patients with a diagnosis of dementia and 225,574 patients without a diagnosis of dementia, all aged 55 and over and registered with UK GPs contributing data to the QResearch database, between 1 January 2004 and 31 January 2016.

The study findings showed increased risks of dementia for anticholinergic drugs overall and specifically for the anticholinergic antidepressants, antipsychotic drugs, antiparkinsons drugs, bladder drugs and epilepsy drugs after accounting for other risk factors for dementia.

No increased risks were found for the other types of anticholinergic drug studied such as antihistamines and gastrointestinal drugs.

Professor Tom Dening, Head of the Centre for Dementia at the University of Nottingham and a member of the research study team, said: "This study provides further evidence that doctors should be careful when prescribing certain drugs that have anticholinergic properties. However, it's important that patients taking medications of this kind don't just stop them abruptly as this may be much more harmful. If patients have concerns, then they should discuss them with their doctor to consider the pros and cons of the treatment they are receiving."

The 58,769 patients with dementia had an average age of 82 and 63% were women. Each dementia case was matched to five control patients of the same age, sex, and general practice.

Anticholinergic drug exposure was assessed using prescription information over a complete period of 10 years from 1 to 11 years before diagnosis of dementia or the equivalent dates in control patients, and was compared between the two patient groups. Further analysis looked at prescriptions for anticholinergic drugs up to 20 years before diagnosis of dementia.

This is an observational study so no firm conclusions can be drawn about whether these anticholinergic drugs cause dementia, and it is possible that the drugs were being prescribed for very early symptoms of dementia.

Professor Coupland said: "Our study adds further evidence of the potential risks associated with strong anticholinergic drugs, particularly antidepressants, bladder antimuscarinic drugs, anti-Parkinson drugs and epilepsy drugs.

"The risks of this type of medication should be carefully considered by healthcare professionals alongside the benefits when the drugs are prescribed and alternative treatments should be considered where possible, such as other types of antidepressants or alternative types of treatment for bladder conditions. These findings also highlight the importance of carrying out regular medication reviews.

"We found a greater risk for people diagnosed with dementia before the age of 80 which indicates that anticholinergic drugs should be prescribed with caution in middle-aged people as well as in older people."

These results, along with those of a similar study published in 2018 help to clarify which types of anticholinergic drug are associated with the highest risks of dementia.

In the 1-11 years before the dementia diagnosis date or equivalent in controls, nearly 57% of cases and 51% of controls were prescribed at least one strong anticholinergic drug, with an average of six prescriptions in cases and 4 in controls. The most frequently-prescribed types of drugs were antidepressants, anti-vertigo and bladder antimuscarinic drugs—which are used to treat an overactive bladder.

The increased risk associated with these drugs indicates that if the association is causal around 10% of dementia diagnoses could be attributable to anticholinergic drug exposure, which would equate to around 20,000 of the 209,600 new cases of dementia per year in the UK.

This is a sizeable proportion and is comparable with other modifiable risk factors for dementia, including 5% for midlife hypertension, 3% for diabetes, 14% for later life smoking and 6.5% for physical inactivity.

CBD Overview

CBD known to be a neuromodulator! However, in terms of cellular physiology, the activities of neuromodulation have not been adequately defined.

QCB modeling has allowed is to identify neuromodulation as the genetic mechanism for enzymatic activity; aka ‘grounding’ for positive and negative interactions between electron and protons as the neutron.

In its role as a neuromodulator, CBD restores “homeostasis” until the disruptive factors creates mutations that necessitate additional CBD to restore equilibrium. In terms of antibiotic properties, it would modulate gram positive and gram negative organisms.

https://www.sciencedaily.com/releases/2019/06/190623143055.htm

Cannabidiol is a powerful new antibiotic

Date:

June 23, 2019

Source:

American Society for Microbiology

Summary:

New research has found that Cannnabidiol is active against Gram-positive bacteria, including those responsible for many serious infections (such as Staphyloccocus aureus and Streptococcus pneumoniae), with potency similar to that of established antibiotics such as vancomycin or daptomycin.

New research has found that Cannnabidiol is active against Gram-positive bacteria, including those responsible for many serious infections (such as Staphyloccocus aureus and Streptococcus pneumoniae), with potency similar to that of established antibiotics such as vancomycin or daptomycin. The research is presented at ASM Microbe, the annual meeting of the American Society for Microbiology.

Cannabidiol, the main non-psychoactive chemical compound extracted from cannabis and hemp plants, has been approved by FDA for the treatment of a form of epilepsy, and is being investigated for a number of other medical conditions, including, anxiety, pain and inflammation. While there is limited data to suggest Cannabidiol can kill bacteria, the drug has not been thoroughly investigated for its potential as an antibiotic.

Work led by Dr Mark Blaskovich at The University of Queensland's Institute for Molecular Bioscience's Centre for Superbug Solutions, in collaboration with Botanix Pharmaceuticals Ltd, an early stage drug discovery company investigating topical uses of synthetic cannabidiol for a range of skin conditions, found that Cannabidiol was remarkably effective at killing a wide range of Gram-positive bacteria, including bacteria that have become resistant to other antibiotics, and did not lose effectiveness after extended treatment.

"Given cannabidiol's documented anti-inflammatory effects, existing safety data in humans, and potential for varied delivery routes, it is a promising new antibiotic worth further investigation," said

Dr. Blaskovich. "The combination of inherent antimicrobial activity and potential to reduce damage caused by the inflammatory response to infections is particularly attractive."

Importantly, the drug retained its activity against bacteria that have become highly resistant to other common antibiotics. Under extended exposure conditions that lead to resistance against vancomycin or daptomycin, Cannabidiol did not lose effectiveness. Cannabidiol was also effective at disrupting biofilms, a physical form of bacteria growth that leads to difficult-to-treat infections.

The project was co-funded by Botanix and Innovation Connections, an Australian government grant scheme to commercialize new products, processes and services. The paper will be presented on Sunday June 23rd from 11am-1 pm at the annual conference of the American Society for Microbiology, ASM Microbe 2019, at the Moscone Convention Center in San Francisco.

Story Source:

Materials provided by **American Society for Microbiology**. *Note: Content may be edited for style and length.*