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Science AMA Series: We're scientists from the Brough Lab at the University of Manchester and we recently found that a commonly used period medication is effective against rodent models of Alzheimer's disease, Ask Us Anything!

Brough$_{L}ab$[1]$andr/ScienceAMAs$[1]

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April 17, 2023

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Would it need to be taken preventatively or after the fact? Also, isn't long-term usage of NSAIDS bad for your GI tract?

StinkinFinger

NSAIDs are drugs which inhibit two enzymes (COX1 and COX2) which are key to the production of inflammation signalling molecules called eicosanoids. We found that fenamates, a subclass, of NSAIDs also inhibit another inflammation signalling pathway that may be important in Alzheimer's disease (interleukin 1 beta). But you both are right, fenamate NSAIDs still inhibit the COX enzymes and this is associated with side-effects. Two of these side-effects are the thinning of the stomach lining and an increased risk of cardiovascular events such as stroke and heart attack. Interestingly, inhibiting COX1 seems to cause the stomach issues and COX2 inhibition is correlated with stroke and heart attack. What's really good is that fenamates appear to be at the mildest end of the NSAID side effects list. Mefenamic acid appears to have less stomach effects than the well tolerated aspirin (https://www.jstage.jst.go.jp/article/jphs1951/48/3/48_3_317/_pdf) and is on the lower end of risk for cardiovascular events, around about a risk of 1.25 fold higher than normal (http://stroke.ahajournals.org/content/41/9/1884.long). While stroke is a concern and difficult to mitigate, the effects on stomach lining can be reduced with drugs which lower the production of acid in your stomach or coatings on the pill which lowers the effects of the fenamates on the stomach. Furthermore, when you do the appropriate calculations a 25mg/kg/day dose in a mouse is predicted to be about 152 mg dose for a 75kg person. This is less than one pill a day and should hopefully confer a very low risk of side effects. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4804402/

Jack

Would it need to be taken preventatively or after the fact? Also, isn't long-term usage of NSAIDS bad for your GI tract?

StinkinFinger

In terms of whether the drugs would need to be taken preventatively we don't really know that. The mouse model we used suggested that the drugs may be effective in patients with early stages of the disease (we used mice at an age where they were just starting to develop pathology). Having said that we are looking into whether fenamate NSAIDs could be preventative too so we may have a better idea in the relatively near future!

Mike

Ahoy!

Alzheimer's like, my BIG phobia. I'm young yet, but every "old" relative of mine got it, so I know I'm quite doomed... in the long term.

I dunno if this is the perfect topic for it but : --what are good way to prevent Alzheimer first hand? I mean, there are probably actions that causes these inflammation you spoke of to happen at larger scale or quicker or sooner, and those actions might be avoided ? --what are good training for the brain that might help it become more resistant to these inflammation?

There have been many claims that "cure", or "vaccines" or "medications" have been "on the verge of being discovered". Could you do us a small summary of what are the more likely cure to arise soon? (In addition to yours of course).

Also, many many many thanks to you guyz for working on that. I guess almost every one knows someone who suffered of it and there's nothing that scares me more than losing memories to the point of being unable to recognize loved ones or treasured books or even words. A cure to Alzheimer would mean as much to me as walking in the stars, really.

So, thanks.

DoctorPrisme

Hi there,

Alzheimer's preventatives are a really sticky area. As you've said yourself the disease is so so horrible and, kind of as a result of this, people are often willing to try anything that might help prevent it. Although there has been some suggestion that things such as Sudoku or brain training games may prevent the disease, these ideas have been largely debunked (great blog - https://www.sciencebasedmedicine.org/ftc-slaps-down-brain-training-claims/#more-40248).

Having said that, there is also pretty good evidence that people who know two languages or stay in school longer do have a reduced risk of getting the disease. In terms of other ways to prevent Alzheimer's there is evidence that eating healthily (leading to healthy heart) leads to a reduced risk.

Either way these kinds of studies are really really hard to run and interpret. Researching a disease that appears so late in life means you have to correct for so many things you often have no idea if your correlation is in any way causal. Additionally, you might find that relatively healthy people get Alzheimer's just because they have lived long enough not to die from something else.

TL;DR there's nothing we can categorically say will prevent Alzheimer's but you might as well eat healthily and live a healthy life anyway.

As for the question RE cures/vaccines/medications woah well that's a huge question! I can't really fully answer that in a comment here but have a look at this recent review for an idea of what has been tested. If you can't access it let me know and I can PM you a PDF.
http://www.sciencedirect.com/science/article/pii/S0028390813003195

Mike

How do you go about selecting the drug to trial? Was there some existing research that suggested a link?

PeterGoddard

There are a few different parts to this question so I'll split it up. First I'll answer how we got to testing fenamate NSAIDs then I'll go into why we chose mefenamic acid.

There a quite a few epidemiological studies suggesting NSAIDs may be protective in Alzheimer's disease. Also, there is increasing evidence that a large protein complex called the inflammasome may contribute to Alzheimer's disease. There is some evidence in the literature that the fenamate class of NSAIDs may inhibit the inflammasome (although this was published years before the inflammasome was discovered). We made this link and thought that fenamates may inhibit the inflammasome and, as a result, be potential treatments for Alzheimer's disease.

As for how we chose mefenamic acid – we've tested a number of different NSAIDs which differed to varying degrees in terms of how effective they were at inhibiting the inflammasome and how clinically available they were. Although not our most potent inhibitor, mefenamic acid was a good inhibitor and, more importantly, is still readily prescribed and researched so we thought our best bet was to progress our study into animal models with mefenamic acid.

Mike

Your sample size for the study was only 20 mice - do you think a small sample size may cause some problems in terms of the potential accuracy of your findings?

Stamford10

The sample size of ten per group was chosen based on statistics and some choices we made balancing getting a statistically significant result and how big an effect size we wanted to look for. This is called a power analysis.

Here is the basic idea. Imagine I gave a coin and I asked you to find out if the coin is biased to heads or tails, what would you do?

You would need to plan how sensitive you want your experiment to be. You might flip it 1000 times and get 501 heads and this may represent the true bias of the coin, but it could easily be chance. If you flipped it a million times and 501,000 heads then you would then be more sure of the bias suggested from the original study but your arm would be very tired. However, if you said I am only looking for a big effect size, then you would need to flip the coin less often. If you flipped the coin 50 times and got 50 heads, you'd be very sure that the coin is bias. Our study in mice was looking for a large effect size. We did statistical analyses based on previous data to estimate the variability of the data and found that a sample size of 10 would be sufficient to find a large effect size. Fortunately, the drugs had a very large effects size and this was found to be statistically significant.

Jack

I'm wondering... Is it considered proved now that inflammation damages the brain in AD?

I tought it was still quite controversial the role of inflammation in this neuropaty

lucaxx85

Evidence for the role of inflammation in Alzheimer's disease progression has been building over the past two decades (1). Histological analyses of brain tissues and clinical imaging techniques of

Alzheimer's disease patients has identified neuroinflammation as a correlative factor with disease severity (2,3); genetic studies have identified a number of mutations in immune regulatory genes as risk factors for Alzheimer's disease (4); animal models of the disease have demonstrated knocking out key genes involved in the inflammatory response slows the progression of the Alzheimer's disease - like phenotype (5,6); and perhaps most convincing of all, epidemiological studies have demonstrated very strong negative correlations with anti-inflammatory use due to unrelated conditions, such as arthritis, and Alzheimer's disease incidence (7). In these studies rates of Alzheimer's disease in sub-populations who had high use of nonsteroidal anti-inflammatory drugs (NSAIDs) had considerably lower incidence of Alzheimer's disease (~50% less) (7).

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For us who might not understand everything, does this mean that we could potentially have a cure for Alzheimer's in the next few years?

SeismicWhales

Despite what you may find in the media we really have very little idea how close we are to a 'cure'. The use of the word cure here is a bit tricky seeing as what we are mostly likely to find in the short term are treatments that slow or delay the progression of the disease rather than prevent or reverse it altogether. Having said all that, the fact that Alzheimer's is such a devastating disease that is affecting so many people at such a rate does mean there is a huge amount of research going into finding such treatments. This means that, although Alzheimer's is a horrible disease, we're giving ourselves the absolute best chance of finding a treatment as quickly as possible! Sorry not to be able to give you a definitive answer.

Mike

For your in vivo studies were you able to look at any of the pathological hallmarks of AD, such as Neurofibrillary Tangles or Amyloid Beta deposition? I know you show microglia inactivation, but did it translate to worsening pathology? I am not as well versed in the deposition patterns of the 3xTG model, but I know in many other models that we use the subiculum aggregates plaques pretty extensively. Did this trend continue in other regions?

scoodles

At this age in the 3xTG model we've found that you might have two or three plaques in the whole mouse and these will be in the subiculum (hence why the hippocampus and cortex results are in the supplement). We didn't look for changes in plaque burden because the statistical power would probably not be there for seeing a drop from two plaques down to one. We are looking at repeating the study in a different mouse model which has a more aggressive pathology. From this we'll look for

changes in plaque burden and phos-tau around the plaques. Always nice to confirm a result in more than one mouse model of AD as well.

Jack

Have you looked at the prevalence of Alzheimer's in regular NSAID takers? Is there a significant reduction in Alzheimer's for those users?

randomwormgenerator

Hi there,

We've answered this in a few different forms in a few questions!

https://www.reddit.com/r/science/comments/54k0af/science_ama_series_were_scientists_from_the/d831ucs
https://www.reddit.com/r/science/comments/54k0af/science_ama_series_were_scientists_from_the/d834624

https://www.reddit.com/r/science/comments/54k0af/science_ama_series_were_scientists_from_the/d833625

Cheers!

Is there a higher correlation of Alzheimer's in those people with inflammatory diseases (IBD's, RA, ect.)?

Do steroidal anti-inflammatory drugs (prednisone or decadron) reduce the incidence of Alzheimer's?

I suspect that the answer to this next question is no, but... With Alzheimer's currently only diagnosable postmortem (vs other types of dementia), does mefenamic acid have any benefit for non Alzheimer's dementia?

FLMurse

It is a bit of a contentious issue and it may come down to the statistics used.But this study was done very thoroughly and is not a cross-sectional study but a cohort study, which is generally considered less susceptible to bias.

From this they found that people with rheumatoid arthritis were about 2.5 times more likely to develop Alzheimer's. Other analyses have tried to group together all the studies done on this topic (about 5 studies) and they found on average the studies reported that rheumatoid arthritis sufferers were 1.8 times more likely to develop Alzheimer's disease. However, people with osteoarthritis generally don't have inflammation in their joints but do take NSAIDs (anti-inflammatories) for their pain relieving effect, and this group of people is about 50% less like to develop Alzheimer's disease. Which is really interesting and it fits with our hypothesis (1).

Steroids were considered for a time butclinical trials found that it actually worsened memory deficits and there were other unwanted side-effects. Part of the problem is that steroids affect many systems of the body including the potentially good activity of the immune system such as cleaning up debris. We think that fenamates inhibit the inflammatory activity of your immune system without inhibiting the good functions of the immune system.

We think inflammation may be involved in many forms of dementia. However, we have not researched this particular drug target in these forms of dementia. We will be looking into it, so keep an eye out for more research into other forms of dementia!

(1) McGeer, P.L., Schulzer, M. & McGeer, E.G. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. Neurology 47, 425-432 (1996

Jack

With it being such a commonly used class of drugs. It is possible to use current Alzheimer's patients prior health records (with consent of course) and look for a negative correlation within that class of drugs? It seems like that would point to an NSAID or two with promise. I understand that is basically what lead to your studying NSAIDs,but have we already data mined as much granularity of detail we can? Another study focusing just on records with various NSAIDs used wouldn't provide any more insight?

nomorecashinpolitics

That's exactly what we are doing now!! Although there is data suggesting that patients on the NSAID class of drugs are less likely to develop Alzheimer's there's been no further research into the fenamate subclass. We're trying to find out whether people that have been taking the fenamate NSAIDs specifically (as opposed to non-fenamates such as ibuprofen or celecoxib) will have a comparatively slower progression of the disease.

Mike

First you dont have to know exactly what causes the problem in order to solve it ? I mean is cure or it could be just a way to minimez temporarly the effects ? And so for the actual question, why we cant found specifically what causes it (regarding the fact that the brain is big mess) ?

Looking forward to the results, thanks

LifeInPlastic_

You're right we don't know exactly what the problem is. We do however have a pretty good bet that inflammation is definitely involved (see Jacks comment!). The drugs we have worked on probably won't cure the disease. What they might do however is slow the progression in someone who is just starting to present symptoms. This may give them more time to find a drug that can reverse the symptoms! The major benefit of these drugs is that they are already available and on the market so moving them into Alzheimer's patients should be much faster and cheaper than starting with a new drug from scratch! In terms of why we don't know what's going we are learning more and more. The main issues surrounding Alzheimer's research are that this doesn't occur naturally in rodents (so it's hard to model and test on), it occurs at a late stage in humans (so if we do research it there are loads of confounding factors that come from just being so old) and that it occurs in the most complicated organ in the body, the brain, which we can't x-ray, biopsy or computer model like we can other organs. We're getting there though so watch this space!!

Mike

How would you suggest I get to where you are now? I am currently new to college and pursuing a degree in biochemistry with a career as a medical researcher in mind. How did you get to where you are and how can I do the same? Thanks in advance for this AMA.

Insomniac199

Hey! Great to hear you're interested in pursuing a career in science. It really is one of the most rewarding jobs out there and I can definitely say both Jack and I absolutely love what we do. You're definitely doing it right so far, the next thing you need to do (mega important) is get some experience in a research lab in college (you may have to beg for this one) then you can look into applying for a PhD. Once you've done that (easy enough… Right?) you've got to keep working and publishing papers to stay in the game. Good luck!!

Mike

What dosage amount of mefenamic acid would this correlate to in humans?

If I currently had Alzheimer's, (I don't), what negative side effects should I be most concerned about if I started taking Ponstel at a doses roughly equivalent to this trial?

j0wc0

What dosage amount of mefenamic acid would this correlate to in humans? If I currently had Alzheimer's, (I don't), what negative side effects should I be most concerned about if I started taking Ponstel at a doses roughly equivalent to this trial?

Jack has covered the answer to these pretty effectively in previous comments:

https://www.reddit.com/r/science/comments/54k0af/science_ama_series_were_scientists_from_the/d831kjl
https://www.reddit.com/r/science/comments/54k0af/science_ama_series_were_scientists_from_the/d831by1

TL;DR After some fancy calculations it correlates to less than a pill a day. Main side effects are gastrointestinal but there are ways around this and they may not be as bad as you might think.

Mike

Does cholesterol medication in any way contribute to Alzheimer's?

TheGlassStone

Interestingly, the age-specific incidence of Alzheimer's disease is decreasing. What this means is that less 85 year olds (for example) are getting Alzheimer's disease. But because there is a growing number of 85 year olds, over all there are more people with Alzheimer's disease. So the question is… why are fewer 85 year olds getting Alzheimer's? We think one reason is that doctors are controlling blood pressure and cholesterol way better than they used to, including the use of statins. Although, this is very difficult to pick out because of the complicated nature of population studies. Overall, the general guideline is happy heart, happy brain. Eating healthy and controlling your blood pressure and cholesterol is a good idea for your health and most-likely dementia.

Jack

How many compounds did you test before making this discovery?

adenovato

Hi there! Whereas a lot of the pharmaceutical companies searching for a treatment are screening huge numbers of compounds at an alarming rate we don't have the capabilities to do that. What we do have however is a pretty good knowledge of the field and we used that to narrow down the fenamates as a possible hit. The result of all that was that we only tested around 15 NSAID-related compounds for the paper (although that number doesn't include the hundreds of compounds we have tested in the Brough lab over the past number of years and all the drugs we have tested since our fenamate discovery).

Mike