Bad Breaks: how stress and meth use combine to dramatically weaken the blood–brain barrier

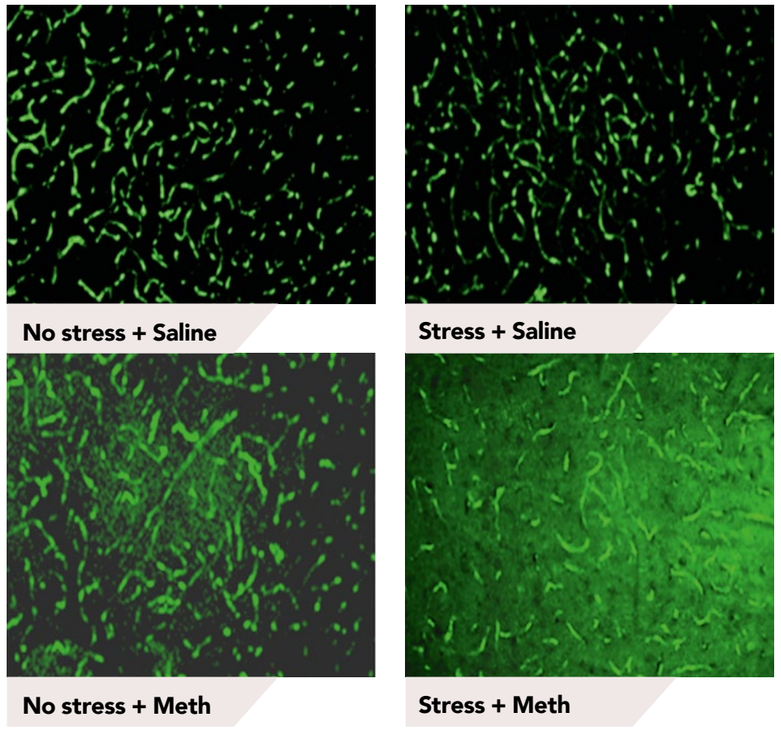
Professor Yamamoto at Indiana University, and his collaborators, are cooking up new explanations for why stress and meth use are a common toxic mix – a mix which breaks down the barrier that protects the brain from potentially deadly toxins and bacteria.

The blood–brain barrier (BBB) is a unique lining of tightly connected cells in all the blood vessels of the brain. This creates a barrier between the cerebrospinal fluid (the liquid which surrounds the brain and spinal cord) and the circulating blood; this barrier is impervious to large, hydrophilic (water-soluble) molecules and bacteria. It allows the passive passage of lipid-soluble molecules and gases, such as oxygen and carbon dioxide, and contains proteins which provide an active transport system for essential nutrients such as glucose. This protects the brain from the majority of large and potentially toxic molecules which might be dissolved in the blood, whilst providing all the substances necessary for normal brain function. It is a unique feature of the blood vessels of the brain, not found anywhere else in the body. This barrier has a distinctive purpose and its correct functioning is vital to human health.

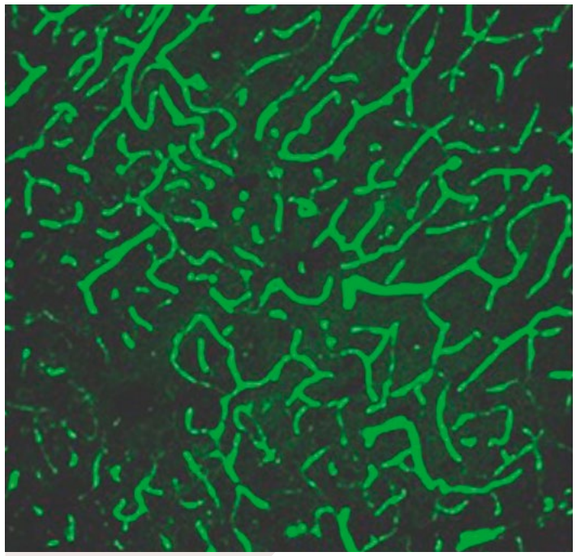
Methamphetamine, n-methylamphetamine known colloquially as 'meth', is a potent psychoactive stimulant used as a recreational drug. For this reason, its use and supply are heavily restricted in most countries. It is well-known to be a highly addictive drug but the damaging effects that it can have on the brain extend beyond addiction and are less widely-known. This neurotoxicity (potential for damaging the brain) is well documented and is a significant factor in its removal from use as a therapeutic drug, and subsequent restriction in an attempt to prevent recreational use. Despite this, its misuse is prevalent across Asia and the United States of America, leading to the requirement to better understand the patterns of use and potential for causing disease.

BREAKING DOWN THE BARRIER

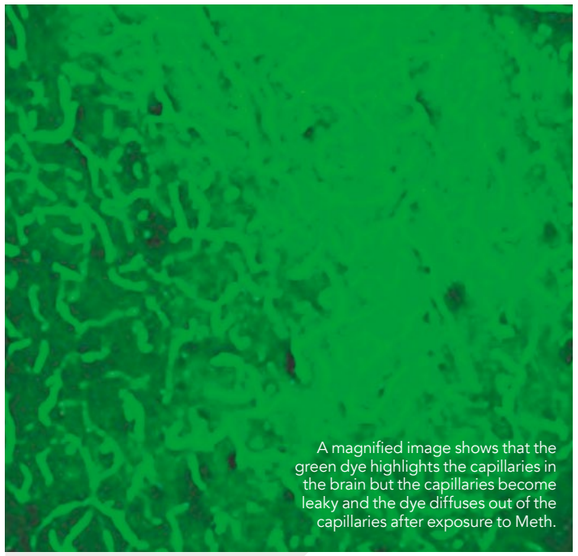
A number of factors are known to affect the tight junctions of epithelial cells in the BBB (special proteins that hold the cells close together to restrict diffusion between them). Ischemic stress associated with stroke is one such factor, and it is this which has provided the key to Prof Yamamoto's work. Ischemic stress (a state of low oxygen that is deadly for cells) results in neuroinflammation, the release of signalling molecules in the brain in much the same way as when any other part of the body is damaged and becomes sore



The green fluorescence is restricted normally to the brain capillaries but diffuses out of the capillaries into the brain tissue when exposed to Meth. This effect of Meth is exacerbated when combined with chronic stress.



A. Intact BBB



A magnified image shows that the green dye highlights the capillaries in the brain but the capillaries become leaky and the dye diffuses out of the capillaries after exposure to Meth.

B. Permeabilized BBB

Q&A

What first attracted you to the research of drugs of abuse and addiction?
My research background is in neurodegenerative disorders and the mechanisms underlying those disorders. The findings that drugs of abuse and addiction produce such pervasive changes in the brain and behaviour prompted me to examine if similar mechanisms underlying neurodegenerative disorders also underlie drugs of abuse.

How will your research help those recovering from meth addiction?
We have applied our thinking about neurodegenerative disorders to problems related to the consequences of meth addiction. We and others are beginning to understand how molecules that play a role in neuroinflammation and neurodegeneration may also be involved in changes that occur within the brain after exposure to meth and that these chemical changes during withdrawal from drug use could be involved in precipitating relapse to drug taking. Therefore, we may be able to curb relapse to drug taking by mitigating the chemical changes that occur during withdrawal from drug exposure.

What is unique about the way you are researching neurological damage from drug abuse?
Past efforts have appropriately focused only on the drug per se, in order to understand how the drug works. However, now that we have a fairly good idea about the action of the drug alone, we can try and model the more realistic situation whereby drug abuse most often co-occurs with a variety of other conditions, such as stress. Thus, we are trying to unravel the complex interactions between stress and drugs of abuse that increase the liability to addiction and brain injury that may not be explainable by simply studying the drug in isolation. Moreover, the traditional line of thinking with regard to drug addiction is that the primary effect is due to the direct action of the drug on the brain. We now have evidence that the action of the drug outside of the brain on peripheral organs can initiate inflammatory processes that are responsible for the drug's neurological effects. Damage to the blood–brain barrier increases the probability that peripheral factors can enter the brain and have neurological effects.

After uncovering the mechanism of neurological damage, what is the next step in developing effective treatments?
Once the mechanisms of the neurological damage are understood, those mechanisms can now serve as targets for possible therapeutics. It is important that there be a clear understanding of the precise mechanisms involved that in turn, could be selectively targeted to avoid untoward side effects of the treatment.

Where do you think drug abuse research will be focused in the future?
An important focus of drug abuse research in the future would be on effective treatment strategies that are based on solid scientific findings. Efforts on strategies that prevent drug addiction are admirable but more efforts directed toward understanding how we treat an established addiction and the relapse to drug abuse are needed.

and swollen. One effect of this is to reduce the concentration of these tight junction proteins, possibly through post-translational modifications, resulting in an increase in permeability of the BBB. The same situation is observed in both stress and acute high-dose meth use; the first through an increase in cyclooxygenase (COX, an inflammation-promoting enzyme), the second through an unknown mechanism which may well be similar to that responsible for meth's neurotoxic properties.

Neuroinflammation is also known to be involved in diseases induced by chronic psychological stress, and chronic stress is known to be associated with increased recreational drug use (known as co-morbidity). Prof Yamamoto's hypothesis is that this chronic stress causes neuroinflammation which, in turn, exacerbates the damage to the BBB caused by meth use. His aim is to now uncover the mechanism by which meth use contributes to BBB damage, with the long-term goal of assessing how these co-morbidities impact on human health over time. Once these effects are understood, there will be an improved knowledge base on which to build effective treatment strategies.

STUDYING STRESS
Prof Yamamoto's group are the first to successfully demonstrate increased neurotoxicity from combined stress and meth use. To date he has also shown that the scope of meth damage is larger than the traditional models of neurotoxicity allow for, with structural damage to the BBB a significant element. He has now begun to show that this structural damage, exacerbated by chronic stress, is persistent rather than transitory – a significant consideration in the treatment of recovering addicts.

By using self-administration regimens of drug abuse in animal models, combined with proven methods of inducing a chronic stress response, Prof Yamamoto's group are able to study this co-morbidity in a unique manner. This method more accurately mimics the situation in human drug abuse situations where self-administration is the norm. It also follows the pattern of drug abuse related to chronic psychological stress, such as in those suffering from post-traumatic stress disorder, where half of long-term sufferers have turned to recreational drug use. By then measuring markers of BBB integrity, such as the concentration of tight junction proteins and the diffusion of fluorescently-labelled molecules of varying sizes, Prof Yamamoto's group will be able to clearly establish the long term effects of this co-morbidity.

REBUILDING THE DEFENCES
Once these mechanisms are established, and the role of COX-mediated neuroinflammation investigated, the group aims to use treatments already shown to combat neuroinflammation to restore BBB integrity. This is important for the treatment of meth abuse, because it has the potential to reduce not only the neurotoxicity associated with the drug itself, but also the associated rise in other neurotoxins in damaged brains and the prevalence of bacterial and viral infections in addicts. A weakened BBB is particularly dangerous in this instance as it is in place specifically for the purpose of preventing the spread of infection to cerebral tissues.

Prof Yamamoto has spent his career fighting against drug abuse in an unusual way, by investigating both its damaging effects and the way it interacts with associated psychological conditions. The fact that drug abuse does not exist in isolation, but rather is precipitated and exacerbated by these conditions, makes this research vital in addressing the health and social impacts of meth abuse in particular. Prof Yamamoto's research is bringing to light previously unknown effects of meth abuse, which promises to have a significant impact on future treatment and therefore recovering addicts' outcomes.

> **Prof Yamamoto's hypothesis is that chronic stress causes neuroinflammation which, in turn, exacerbates the damage to the blood–brain barrier caused by meth use**

Detail

RESEARCH OBJECTIVES
Professor Yamamoto and his team focus their research on the mechanisms behind the toxicity of psychostimulant drugs. In particular, they focus on methamphetamine and MDMA – both widely abused drugs that cause neuronal damage of which little is known.

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BIO
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