Time of day influences our susceptibility to infection, study finds

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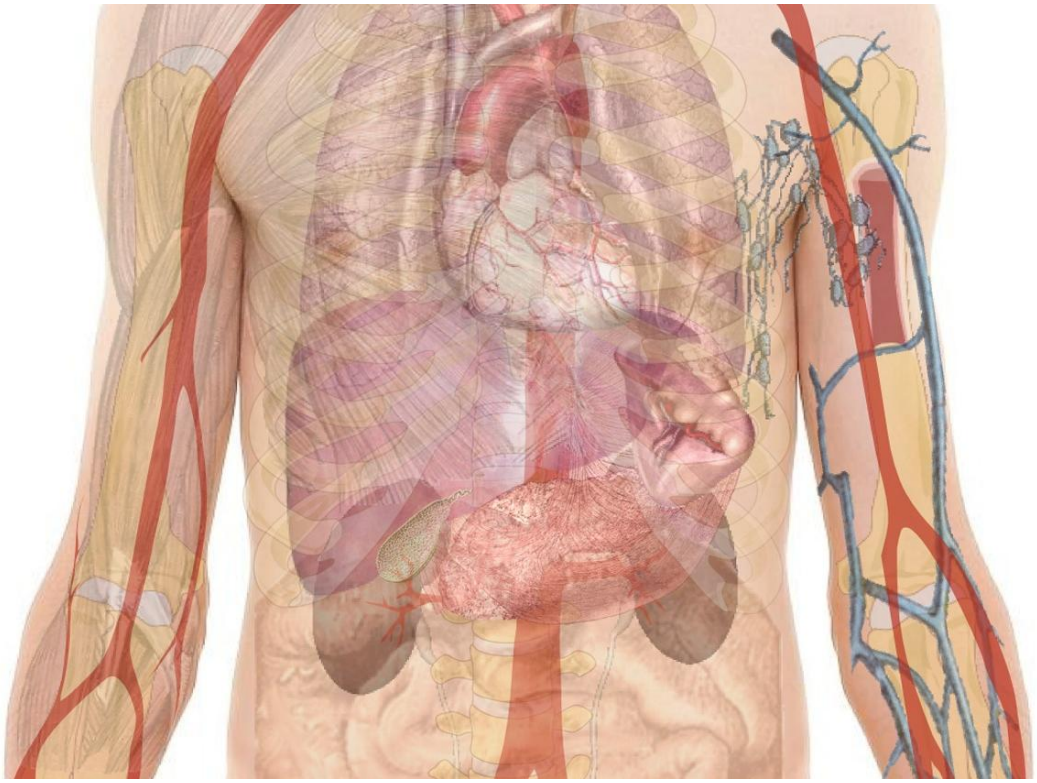

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We are more susceptible to infection at certain times of the day as our body clock affects the ability of viruses to replicate and spread between cells, suggests new research from the University of Cambridge. The findings, published today in the *Proceedings of the National Academy of*

Sciences, may help explain why shift workers, whose body clocks are routinely disrupted, are more prone to health problems, including infections and chronic disease.

When a virus enters our body, it hijacks the machinery and resources in our cells to help it replicate and spread throughout the body. However, the resources on offer fluctuate throughout the day, partly in response to our circadian rhythms - in effect, our body clock. Circadian rhythms control many aspects of our physiology and bodily functions - from our sleep patterns to body temperature, and from our immune systems to the release of hormones. These cycles are controlled by a number of genes, including Bmal1 and Clock.

To test whether our circadian rhythms affect susceptibility to, or progression of, infection, researchers at the Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, compared normal 'wild type' mice infected with herpes virus at different times of the day, measuring levels of virus infection and spread. The mice lived in a controlled environment where 12 hours were in daylight and 12 hours were dark.

The researchers found that virus replication in those mice infected at the very start of the day - equivalent to sunrise, when these nocturnal animals start their resting phase - was ten times greater than in mice infected ten hours into the day, when they are transitioning to their active phase. When the researchers repeated the experiment in mice lacking Bmal1, they found high levels of virus replication regardless of the time of infection.

"The time of day of infection can have a major influence on how susceptible we are to the disease, or at least on the viral replication, meaning that infection at the wrong time of day could cause a much more severe acute infection," explains Professor Akhilesh Reddy, the

study's senior author. "This is consistent with recent studies which have shown that the time of day that the influenza vaccine is administered can influence how effectively it works."

In addition, the researchers found similar time-of-day variation in virus replication in individual cell cultures, without influence from our immune system. Abolishing cellular circadian rhythms increased both herpes and influenza A virus infection, a dissimilar type of virus - known as an RNA virus - that infects and replicates in a very different way to herpes.

Dr Rachel Edgar, the first author, adds: "Each cell in the body has a biological clock that allows them to keep track of time and anticipate daily changes in our environment. Our results suggest that the clock in every cell determines how successfully a virus replicates. When we disrupted the body clock in either cells or mice, we found that the timing of infection no longer mattered - viral replication was always high. This indicates that shift workers, who work some nights and rest some nights and so have a disrupted body clock, will be more susceptible to viral diseases. If so, then they could be prime candidates for receiving the annual flu vaccines."

As well as its daily cycle of activity, Bmal1 also undergoes seasonal variation, being less active in the winter months and increasing in summer. The researchers speculate that this may help explain why diseases such as influenza are more likely to spread through populations during winter.

Using cell cultures, the researchers also found that herpes viruses manipulate the molecular 'clockwork' that controls our circadian rhythms, helping the viruses to progress. This is not the first time that pathogens have been seen to 'game' our body clocks: the malaria parasite, for example, is known to synchronise its replication cycle with

the host's circadian rhythm, producing a more successful infection.

"Given that our body clocks appear to play a role in defending us from invading pathogens, their molecular machinery may offer a new, universal drug target to help fight infection," adds Professor Reddy.

More information: Edgar, RS et al. Cell autonomous regulation of herpes and influenza virus infection by the circadian clock. *PNAS*; e-pub 15 Aug 2016; DOI: 10.1073/pnas.1601895113

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