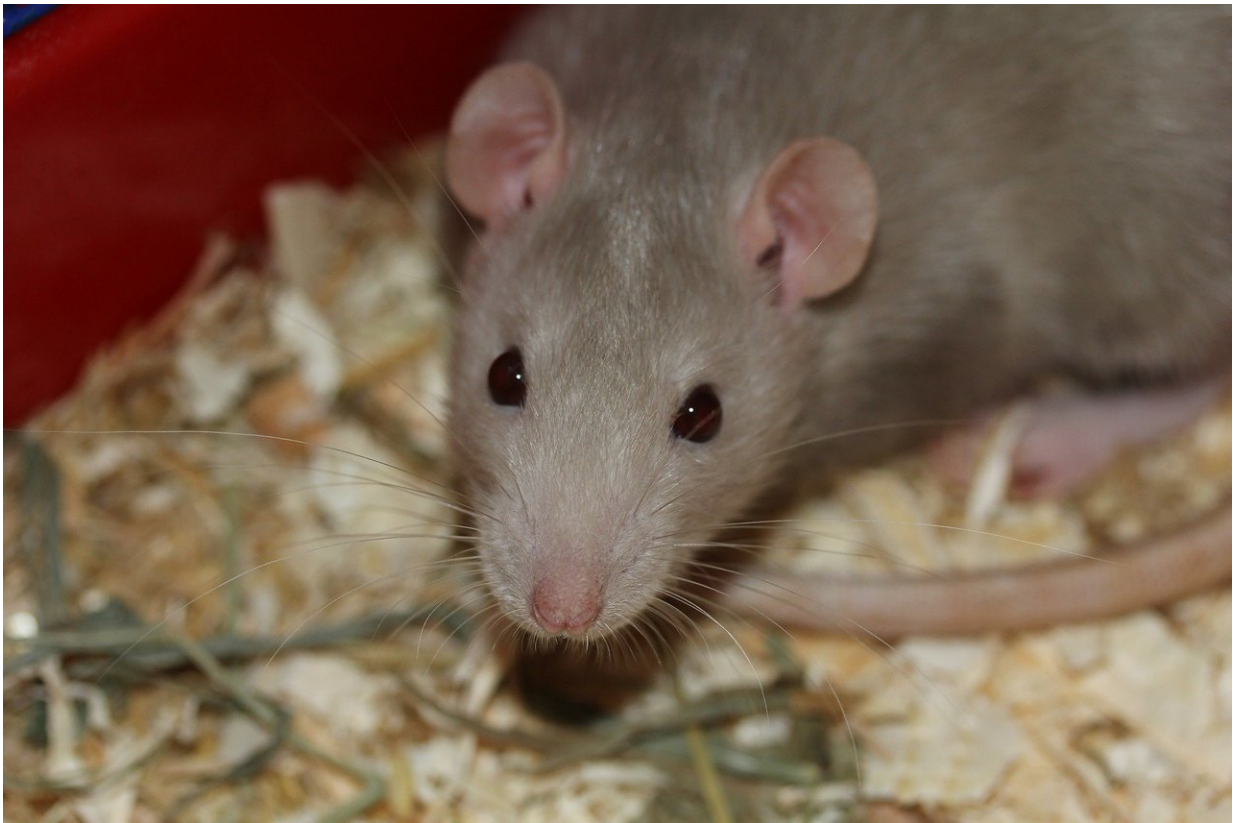


Treatment prevents symptoms of schizophrenia in tests with rats

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Researchers at the Federal University of São Paulo (UNIFESP) in Brazil have tested a sodium nitroprusside treatment on a strain of rats that exhibited some of the symptoms associated with schizophrenia. The

results obtained with this group of adolescent animals suggest that preventive treatment of the disease may be possible for young people considered at risk owing to cases of schizophrenia in their family history—15 percent to 30 percent of risk cases develop the disease later in life.

The principal investigator was Vanessa Costhek Abílio, a professor in the Pharmacology Department of UNIFESP's Medical School (Escola Paulista de Medicina). The findings have been published in the journal *CNS Neuroscience & Therapeutics*.

Schizophrenia is an incurable neuropsychiatric disorder that typically develops in late adolescence or early adulthood. "What if we could develop a safe, preventive treatment for these children so as to avert development of [schizophrenia](#) in adulthood?" Abílio wondered.

Sodium nitroprusside is a salt that acts as a significant donor of [nitric oxide](#), a powerful vasodilator. For this reason, it has been prescribed since the 1920s for severe hypertension. More recently, evidence has been found that it might also benefit patients with schizophrenia. The experiment used rats that spontaneously become hypertensive and also display behavioral alterations. These rats belong to a strain selected in Japan in the 1960s and used since then in animal models of hypertension and cardiovascular problems.

"In 2007, we began performing studies to show that rats of this strain display cognitive problems, poor social interaction and hyperlocomotion—behavioral alterations that model the symptoms of schizophrenia. Our goal was to demonstrate this similarity so that spontaneously hypertensive rats could be used to study schizophrenia," Abílio said.

Thus, the investigation of sodium nitroprusside's preventive effects in

rats was only made possible when researchers were able to identify in animal model traces from schizophrenia's three categories of symptoms.

Agitated body movements, thought disorders, hallucinations and delusions are called positive symptoms. Blunted or flat affect (reduced expression of emotions), poor social interaction, loss of capacity to feel pleasure (anhedonia) and lack of motivation are termed negative symptoms. Cognitive symptoms include difficulty paying attention and problems with working memory.

The occurrence of hallucinations in schizophrenic patients is known to be associated with an increase in levels of the neurotransmitter dopamine in a specific brain region. Higher levels of dopamine are associated with hyperlocomotion in rats.

"All this neurochemistry is well known, so that in preclinical models, when animals display increased locomotion, this is considered evidence of higher levels of dopamine in the limbic region, which is also associated with delusions and hallucinations in schizophrenia," said the researcher.

Results are achieved with daily doses treatment

Laboratory rats considered healthy and rats of the spontaneously hypertensive strain were submitted to two different types of treatment. A single injection of sodium nitroprusside was administered to adult animals (more than 90 days old). Approximately 24 hours later, behavioral tests were performed to verify the occurrence of symptoms such as cognitive impairment, social interaction deficit, and locomotion alterations.

Young animals (aged 30 to 60 days) were treated with daily doses of sodium nitroprusside for 30 days, followed by a one-month interval until

they reached 90 days old and were considered adults. Behavioral testing began at this point.

The spontaneously hypertensive adult rats used in the experiment displayed hyperlocomotion, diminished [social interaction](#), and emotional memory deficit. No behavioral changes were observed following administration of a single dose of sodium nitroprusside.

The most important results of the experiment were observed in the young rats that received the longer-term treatment. The behavioral tests that began 30 days after the injections of sodium nitroprusside ended, when the animals were 90 days old and hence adult, showed that while the treatment had no visible effects on the healthy rats, the spontaneously hypertensive rats failed to display the behavioral alterations in adulthood associated with the symptoms of schizophrenia.

In other words, treatment with sodium nitroprusside prevented the appearance of the behavioral disorders that would have been inevitable without it.

Scientists, however, are still unsure about how sodium nitroprusside acts to prevent the development of symptoms. "That's what we've set out to discover in the new stage of the research," Abílio said. "What we do know is that sodium nitroprusside has an effect on the organism's nitrergic system [neuronal communication mediated by nitric oxide]. Sodium nitroprusside is a donor of nitric oxide, which is a neurotransmitter, a chemical that transmits signals between neurons. Nitrergic neurotransmission is altered in schizophrenia and modulates other neurotransmission systems associated with the physiopathology of the disease. In addition, nitric oxide participates in neurodevelopment-related processes that are altered in schizophrenia."

The administration of sodium nitroprusside in the adolescent stage of

spontaneously hypertensive [rats](#) somehow had a beneficial influence on this entire chain of neurochemical relationships, preventing the appearance of behavioral alterations when the animals reached adulthood.

According to the authors, new studies are needed to investigate whether therapeutic possibilities such as sodium nitroprusside could be used to prevent or attenuate the development of schizophrenia.

An important study by Brazilian researchers published in 2013 in [JAMA Psychiatry](#), a journal produced by the American Medical Association, reported the discovery that administration of sodium nitroprusside has therapeutic effects on the symptoms of patients with severe schizophrenia. Its main contribution was to show that a single intravenous injection of sodium nitroprusside produced rapid improvements in positive symptoms (such as hallucinations), negative symptoms (such as blunted affect), anxiety and depression in patients with severe schizophrenia.

"Hallak's study showed that a single injection of sodium nitroprusside led to a global and lasting improvement in the symptoms experienced by 20 inpatients undergoing treatment for severe schizophrenia," Abílio said.

The discovery led to a number of other studies, and there is now strong evidence for the beneficial effects of [sodium](#) nitroprusside on patients with schizophrenia. "We decided to investigate whether the drug also had a preventive effect on schizophrenia. To do so, we treated the animals before they displayed manifestations of the disease," Abílio said.

More information: Mariana C. Diana et al, Sodium nitroprusside is effective in preventing and/or reversing the development of

schizophrenia-related behaviors in an animal model: The SHR strain, *CNS Neuroscience & Therapeutics* (2018). [DOI: 10.1111/cns.12852](https://doi.org/10.1111/cns.12852)

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