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Laboratory Investigation

LABORATORY INVESTIGATION

Differential role of nitric oxide in the psychedelic symptoms induced by racemic ketamine and esketamine in human volunteers

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Abstract

Background: Animal studies suggest that *N*-methyl-D-aspartate receptor (NMDAR) hypofunction and subsequent decline in intracellular nitric oxide (NO) are responsible for development of ketamine-induced psychedelic symptoms. To examine this mechanism in humans, we administered the NO donor sodium nitroprusside during infusion of racemic ketamine (RS-ketamine), containing equal amounts of S(+)- and R(−)-ketamine isomers, or esketamine, containing just the S(+)-isomer.

Methods: In this randomised, double blind, placebo-controlled crossover study, healthy volunteers were treated with sodium nitroprusside 0.5 μg kg^{-1} min^{-1} or placebo during administration of escalating doses of RS-ketamine (total dose 140 mg) or esketamine (70 mg). Drug high, internal and external perception, obtained using the Bowdle questionnaire, were scored over time on a visual analogue scale. The area-under-the-time-effect-curve (AUC) was calculated for each end-point.

Results: Sodium nitroprusside significantly reduced drug high AUC [mean (standard deviation); placebo 9070 (4630) *vs* sodium nitroprusside 7100 (3320), $P=0.02$], internal perception AUC [placebo 1310 (1250) *vs* nitroprusside 748 (786), $P<0.01$] and external perception AUC [placebo 4110 (2840) *vs* nitroprusside 2890 (2120), $P=0.02$] during RS-ketamine infusion, but was without effect on any of these measures during esketamine infusion.

Conclusions: These data suggest that NO depletion plays a role in RS-ketamine-induced psychedelic symptoms in humans. The sodium nitroprusside effect was observed for R(−)- but not S(+)-isomer-induced psychedelic symptoms. Further studies are needed to corroborate our findings and assess whether higher sodium nitroprusside doses will reduce esketamine-induced psychedelic symptoms.

Clinical trial registration: NTR 5359.

Keywords: esketamine; nitric oxide; psychosis; racemic ketamine; sodium nitroprusside

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Editor's key points

- Reduced neuronal nitric oxide signalling has been implicated in the psychotogenic symptoms of ketamine administration.
- The ability of sodium nitroprusside to reduce the psychedelic symptoms of ketamine was tested in human volunteers.
- Sodium nitroprusside reduced the drug high and the psychedelic symptoms of racemic RS-ketamine but not of S-ketamine infusion.
- Reduced nitric oxide signalling is involved in the psychedelic symptoms of RS-ketamine, while the mechanism of the effects of S-ketamine requires further study.

Ketamine, a non-competitive antagonist of the *N*-methyl-D-aspartate receptor (NMDAR), was designed in the 1960s as a shorter acting alternative to phencyclidine.[1] While initially applied as an anaesthetic in clinical human and veterinarian practice, it is currently also used off-label for treatment of acute and chronic non-cancer pain, opioid-refractory cancer pain, migraine, post-traumatic stress disorder, and major (therapy-resistant) depression.[1–7] Despite its efficacy for multiple indications, physicians are sometimes hesitant when considering ketamine treatment, and patient compliance can be low because of undesirable symptoms.[2,8] In rodents, NMDAR antagonists produce hyperlocomotion, stereotypical or psychotic-like behaviour (including increased urge to run around, inability to hold still with weaving/shaking/twitching of the head and body), and ataxia[9]; in humans, ketamine induces schizotypical or psychedelic effects (paranoia, hallucinations, derealisation, depersonalisation, anxiety) and an intense state of (drug) high.[2,8] As these symptoms mimic schizophrenic behavioural effects, ketamine is successfully used in volunteers as model of schizophrenia.[10,11] Although in patients psychedelic symptoms can be moderated with benzodiazepine or α_2-agonist treatment, complete disappearance occurs when treatment ends.[2,8]

Several mechanisms have been proposed to explain the psychedelic effects caused by ketamine and related NMDAR antagonists, such as decreased gamma-aminobutyric acid B receptor function or altered dopaminergic transmission.[12–14] An attractive hypothesis relates to the model of NMDAR hypofunction. Ketamine binds to the phencyclidine site of the NMDAR, which blocks the inflow of Ca^{2+}-ions.[1,15] Normally, Ca^{2+}-ions that enter the cell in response to glutamatergic NMDAR activation bind to calmodulin that subsequently stimulates nitric oxide (NO) synthase to produce the gaseous neuromodulator NO from L-arginine.[16–18] NO interacts with guanylyl cyclase to generate cyclic guanosine monophosphate (cGMP) from guanosine triphosphate; cGMP subsequently interacts with cGMP-dependent protein kinase and has neuroplastic, neurotrophic, and neuroprotective effects.[16–18] NMDAR antagonism-induced blockade of Ca^{2+}-ion inflow reduces intracellular NO synthesis.[19] Animal studies show that modulation of NO concentrations using mechanisms that bypass the NMDAR can reduce or even prevent NMDAR hypofunction-related psychotic behaviour. For example, in mice and rats, the NO donor sodium nitroprusside blocks phencyclidine- and racemic ketamine-induced psychotic behavior.[20,21] Additionally, sodium nitroprusside can attenuate racemic ketamine-induced memory defects and social withdrawal and has anxiolytic effects.[22] In a recent human study, improvement of schizophrenia symptoms was observed after nitroprusside treatment.[23]

To determine whether NMDAR antagonist-induced psychedelic symptoms are amendable by modulation of the nitrinergic pathway in humans, we tested the effect of sodium nitroprusside i.v. in a healthy population during the infusion of increasing doses of ketamine. Psychedelic effects were measured using the Bowdle questionnaire, a validated list of 13 questions developed for quantifying the psychedelic effects of ketamine in healthy volunteers.[24,25] We applied our paradigm to two ketamine formulations that are currently commercially available for human use, racemic ketamine and esketamine. Racemic ketamine contains equal amounts of two optical isomers, the S(+)- and R(−)-enantiomers; esketamine exclusively contains the S(+)-isomer. Our approach will allow detection of nitroprusside effects specific to S(+)-ketamine, R(−)-ketamine or to both enantiomers. We hypothesise that nitroprusside reduces racemic ketamine- and esketamine-induced drug high (our main end-point) and changes in internal and external perception (secondary end-points).

Methods

Ethics

Participants were recruited after protocol approval was obtained from the Human Ethics Committee at Leiden University Medical Centre (Leiden, The Netherlands) and the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, The Hague, The Netherlands) by flyers posted on the Leiden University campus. All subjects gave oral and written informed consent before participation in the study. The study was registered in the Dutch trial register (www.trialregister.nl) under number NTR 5359. This study is part of a large project on: (1) the pharmacokinetics and pharmacodynamics of racemic ketamine *vs* esketamine and; (2) the influence of sodium nitroprusside on ketamine's effects (psychedelic effects, mood, cardiovascular effects, and pain relief). Here we report on the effect of sodium nitroprusside on the psychedelic effects of the two ketamine formulations currently commercially available.

Subjects

Male subjects, aged 18–34 yr and with a BMI of 30 kg m^{-2} or less, were recruited. Participation was possible after passing a physical examination and after reported absence of any health issues including presence or history of any psychiatric, medical or neurologic disorder, presence or a history of illicit drug use or excessive alcohol consumption (>21 units per week), or known allergies to study medication. Additionally, subjects were excluded from participation if they had a positive drug screen on the day of screening or on any of the study days, had participated in another trial in the 3 months before enrolment, or used any medication on a regular basis (e.g. pain medication). The decision to enrol the subject into the study was made by the independent physician that performed the subjects' screening. Subjects were asked to refrain from food or drinks for 8 h before dosing, not to consume caffeinated food or beverages in the 24 h before dosing, and not to consume any grapefruit-containing food or beverages during the 7 days preceding the study day.