Central administration of interleukin-1β elevates brain kynurenic acid and disrupts PPI

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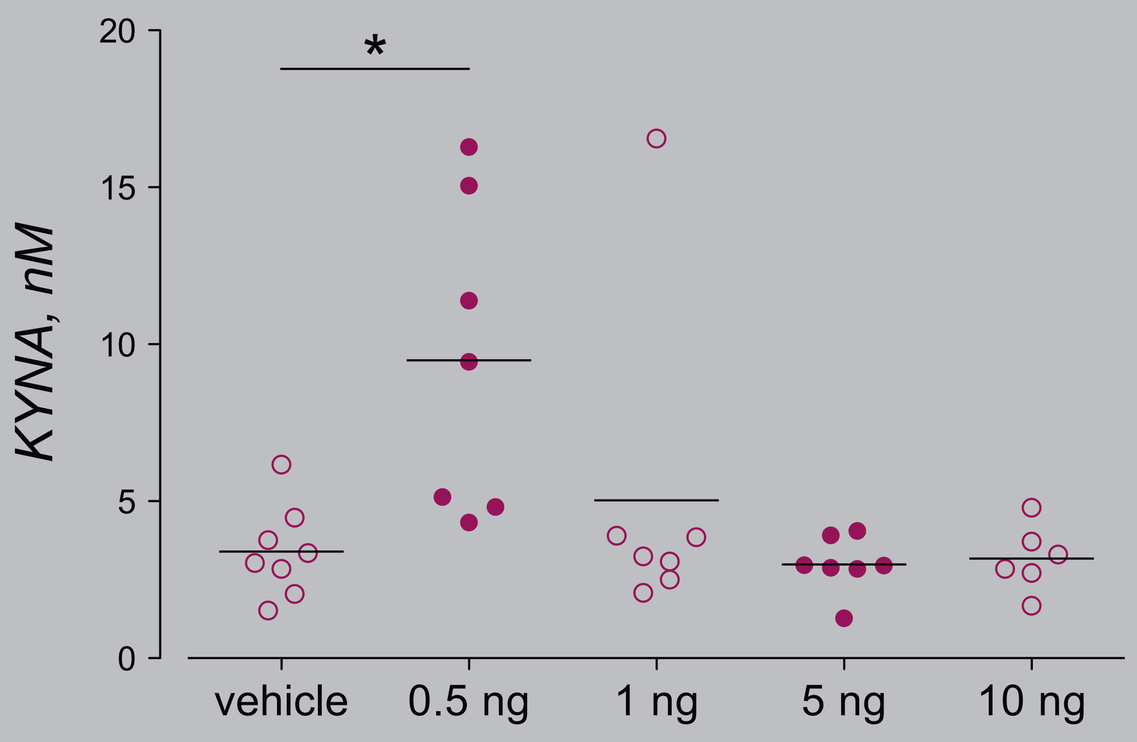
Introduction

Patients with schizophrenia and bipolar disorder display elevated central levels of the pro-inflammatory cytokine interleukin-1β (IL-1β) and of kynurenic acid (KYNA). Both KYNA and IL-1β are predominantly elevated in those bipolar patients that have had a psychotic episode. Moreover, pharmacologically elevated levels of KYNA in rodents have been shown to disrupt prepulse inhibition (PPI).

Aim

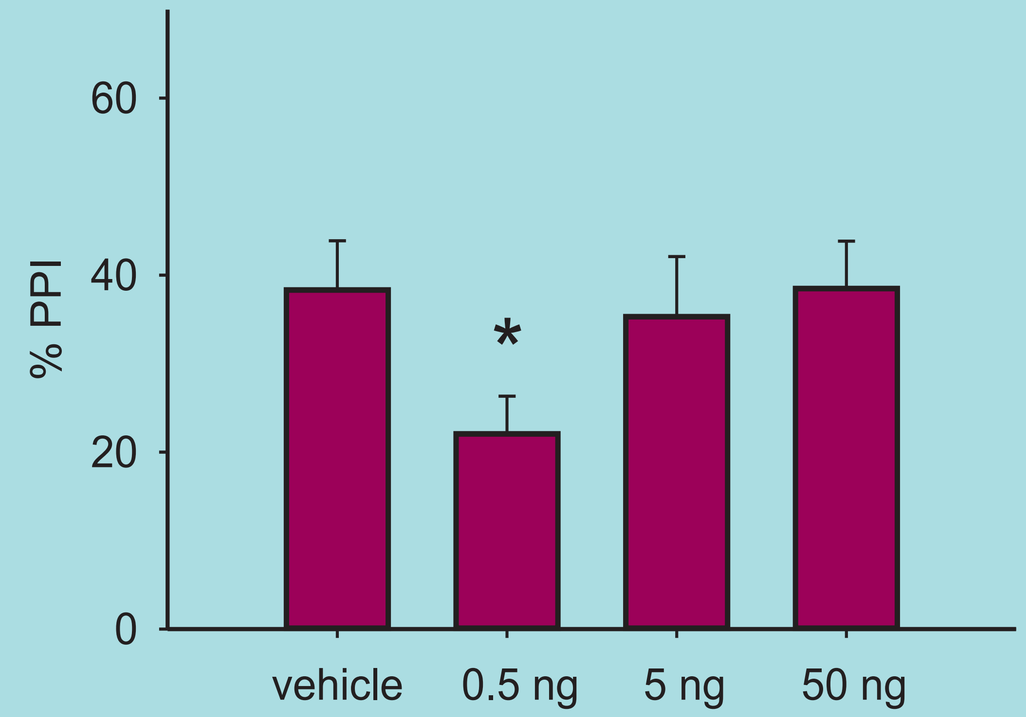
The aim of the present study was to investigate if IL-1β influences the synthesis of brain KYNA in mice and if administration of IL-1β affects PPI.

Interleukin-1β increases brain kynurenic acid

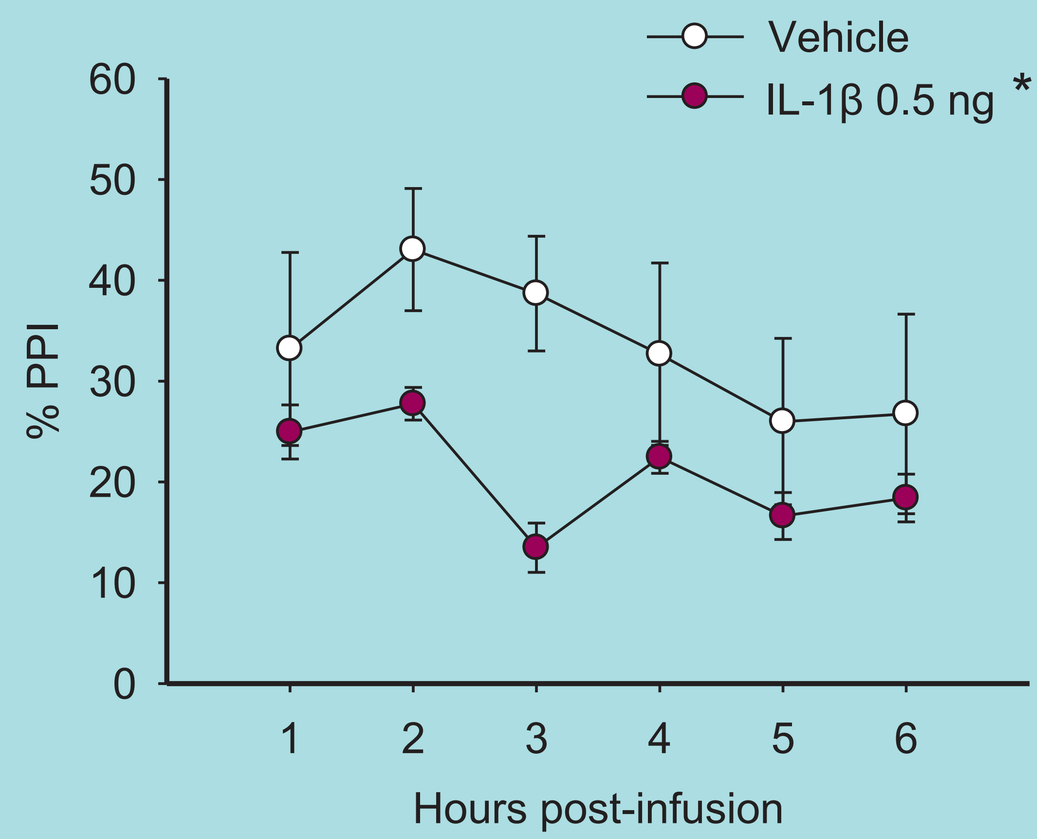


Administration of 0.5 ng IL-1β, but not 1, 5, or 10 ng, significantly elevated brain KYNA levels compared to vehicle 6 h post-injection (9.49 ± 1.88 nM vs. 3.40 ± 0.51 nM, $p < 0.05$).

Interleukin-1β disrupts PPI



Dose response of IL-1β on PPI during the ISI block. Data are collapsed across hours 1-3 post-injection. Drug: $F(1,31) = 2.27$, $p = 0.1002$.
* $p = 0.0243$ vs. vehicle.



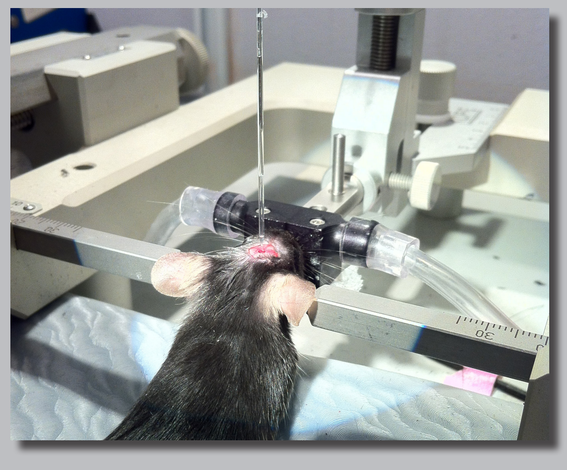
IL-1β disrupted PPI at the 0.5 ng dose. Data are average PPI during the ISI block at every hour over a 6 h period. *Main effect of drug; $F(1,15) = 5.40$, $p = 0.0345$.

Conclusions

Present results support the hypothesis that IL-1β and KYNA are important players in the pathophysiology of psychotic diseases, such as schizophrenia and bipolar disorder.

Notably, only administration of the lowest dose IL-1β disrupted PPI, indicating that this effect may be mediated by the increased brain KYNA concentrations observed at this dose.

Present data are also in line with recent in-vitro data from our laboratory showing that IL-1β, by inducing tryptophan 2,3-dioxygenase, increase KYNA production in human cortical astrocytes.



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Methods

C57BL/6 mice were injected intracerebroventricular (i.c.v.) with 0.5, 1, 5, or 10 ng IL-1β. The animals were sacrificed after 6 hours and brain KYNA was quantified. Another cohort of mice received 0.5, 5, or 50 ng of IL-1β and were tested for PPI deficits at several time points post-injection.

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