Antidepressant-like Effects of Kynurenic Acid Analogues

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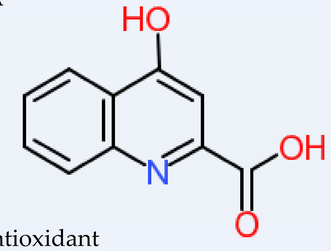
Abstract

- Kynurenic acid (KYNA) - a metabolite of the L-tryptophan (TRP)-kynurenine (KYN) metabolic pathway
- KYNA triggered antidepressant-like effects intracerebroventricularly (i.c.v.) in modified forced swimming test (FST) of mouse
- KYNA is impermeable to the blood-brain-barrier (BBB)
- New KYNA analogues permeable to the BBB in vitro - SZR72, SZR81, SZR104
- KYNA analogues (i.c.v.)
  - SZR72: no effect
  - SZR81: antidepressant-like effect
  - SZR104: no effect
- KYNA analogues intraperitoneally (i.p.)
  - SZR72: no effect
  - SZR81: no effect
  - SZR104: no effect
- KYNA analogues
  - Changed biological properties ?
  - Impermeable to the BBB in vivo ?
  - Peripherally metabolized ?

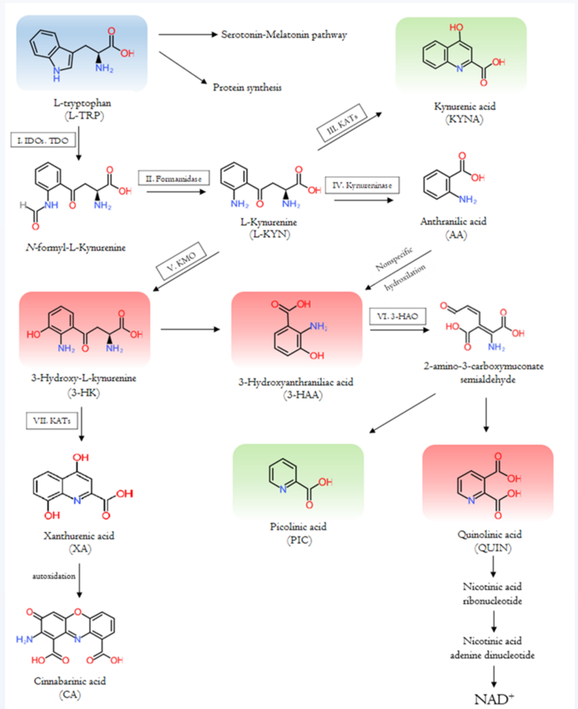
Introduction

- TRP-KYN metabolic pathway
  - > 95% TRP metabolized in the pathway
  - Synthesize various bioactive molecules
  - Oxidants, antioxidants
  - Neurotoxins, neuroprotective
  - Immunomodulators
- KYNA



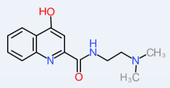
  - Antioxidant
  - Neuroprotective
  - Antidepressant-like
  - KYNA impermeable to the BBB

Tryptophan (TRP)-Kynurenine (KYN) Metabolic Pathway

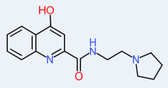


Materials and Methods

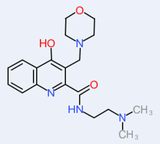
- Ethics: The Committee of Animal Research at the University of Szeged (I.74-24/2018) and the Scientific Ethics Committee for Animal Research of the Protection of Animals Advisory Board (XI./240/2019)
- Charles Dawley (CD) 1 male mice
- 15 mins pretest 24 hours before
- i.c.v.. administration 30 mins before behavior sampling
- i.p.. administration 30 mins before behavior sampling
- Open field (OF) test
- one-way ANOVA
- SZR72



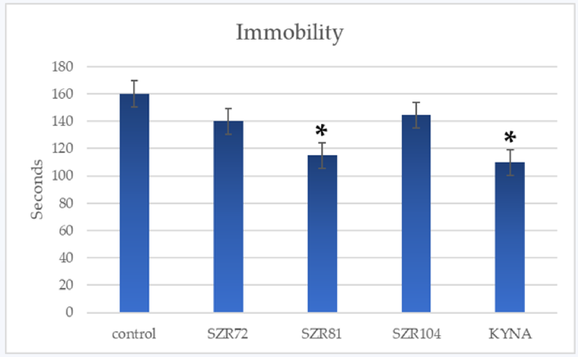
- SZR81

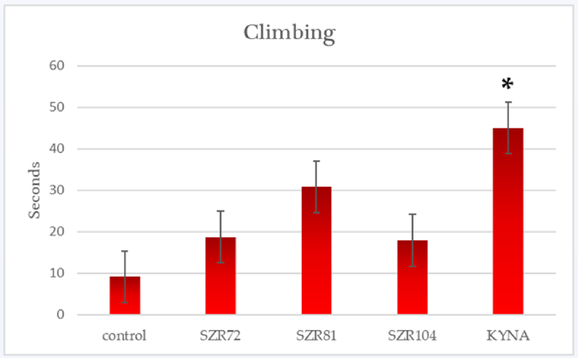


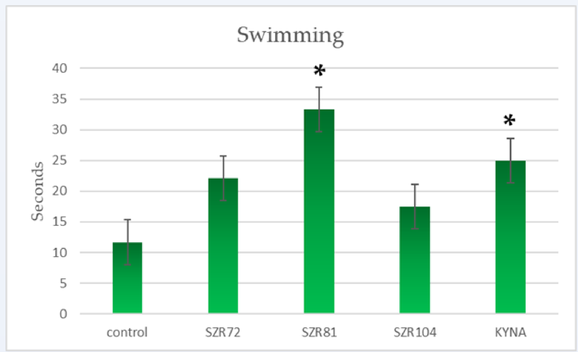
- SZR104



Results







- SZR 81 and KYNA decreased immobility time (i.c.v.)
- KYNA increased climbing time (i.c.v.)
- SZR81 and KYNA increasing swimming time (i.c.v.)
- No significant changes after i.p. administration
- No significant changes in OF test

Conclusion

- i.c.v. administration of SZR81 significantly decreased immobility time and significantly increased swimming time
- The antidepressant-like effects were triggered at least in part through the serotonin 5-HT nervous system
- SZR72 and SZR104 may have lost original biological activities upon i.p. administration
- SZR72 and SZR104 may not cross the BBB in vivo
- Findings in this study may be limited to the dose tested

	Antidepressant-like effects	
	i.c.v	i.p.
KYNA	+	-
SZR72	-	-
SZR81	+	-
SZR104	-	-

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