Exploring neurocognitive mechanisms underlying losartan-augmented prevention of posttraumatic stress symptom development

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Background

- In a human patient cohort study patients on hypertensive medication targeting the renin-angiotensin system (such as 'losartan') developed fewer PTSD symptoms after trauma compared to patients on other hypertensive medication¹
- This study aimed to investigate the underlying neurocognitive mechanisms by looking at peritraumatic processing
- Cognitive models of PTSD propose that the disorder might develop due to an excess of amygdala-based low-level data-driven processing and a lack of hippocampal higher-level contextual processing during trauma exposure²
- Animal studies confirm that losartan affects amygdala-based stress responses and hippocampal memory performance^{3,4}

Hypotheses

Primary

Decrease in data-driven processing and/or increase in contextual processing after losartan administration

Secondary

Reduction in analogue trauma symptom development in the losartan group

Methods

- N = 40 (26 female) healthy volunteers, double-blind
- Pharmacological manipulation (50mg losartan vs. matched placebo)
- After 1hr: Analogue trauma induction using trauma-film paradigm and monitor heart rate during film presentation
- Peritraumatic processing task: Blurry pictures which increasingly become clearer (pictures of trauma film and negative match)

- Rating of descriptions of film images also included details not presented in the image itself, but only during film presentation
- Analogue trauma symptoms measured via intrusion diary for four consecutive days and follow-up questionnaires
- Data-driven processing analysed using 2x2 mixed-Model ANOVA (trauma, neg match x placebo, losartan); contextual processing analysed using paired samples t-test

Results

Primary

- Losartan prevents an increase of heart Rate during film presentation compared to the placebo group ($t(26.14) = 2.26, p = .032, d = .44$).
- No main effect or interaction effect in data-driven processing ($ps > .132$), but enhancement in contextual processing in the losartan group (trauma condition: $t(38) = -3.75, p = .001, d = -1.15$).
- Losartan group reported more details per second in the negative match condition ($t(38) = -4.40, p = .022, d = -0.80$).

Data-driven processing

Contextual processing

Fig 1: Performance in the peritraumatic processing task (mean and SE); * $p < .05$; ** $p < .01$

Secondary

- No differences in analogue trauma symptom development between the groups (all $ps > .234$), contrary to our expectation

Discussion

- No effects on analogue symptoms, possibly since a single dose was too small to obtain effects on symptom level.
- Drug may have reduced arousal in response to threatening material indicated by the stable heart rate.
- Losartan enhanced perceptual processing of trauma-related cues, reflected in perceiving more details in negative match images. Possibly a mechanisms enhancing discrimination between safe and trauma cues.

Conclusion

- First evidence that losartan affects how people process traumatic events.
- Promising mechanisms are stable peritraumatic physiological arousal, an increase in contextual processing and an enhancement in visual discrimination of trauma-related cues.
- We did not find effects on analogue symptom level, thus interpretation restricted.

References:

[1] Khoury, N. M., Marvar, P. J., Gillespie, C. F., Wingo, A., Schwartz, A., 2012. The renin-angiotensin pathway in posttraumatic stress disorder: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. *J Clin Psychiatry* 73, 849–855. [2] Brewin, C. R., 2001. A cognitive neuroscience account of posttraumatic stress disorder and its treatment. *Behav Res Ther* 39, 373–393. [3] Llano López, L. H., Caif, F., García, S., Fraile, M., Landa, A. I., 2012. Anxiolytic-like effect of losartan injected into amygdala of the acutely stressed rats. *Pharmacol Rep* 64, 54–63. [4] Bild, W., Hritcu, L., Stefanescu, C., Ciobica, A., 2013. Inhibition of central angiotensin II enhances memory function and reduces oxidative stress status in rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* 43, 79–88.

Disclosure: The authors report no conflict of interest