Ginger root extract mitigates neuropathic pain via suppressing neuroinflammation: gut-brain connection

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ABSTRACT

Objectives: Emerging evidence suggests an important role of the gut-brain-axis in the development of neuropathic pain (NP). We investigated the effects of gingerol-enriched ginger (GEG) on pain sensitivity and mRNA expression of inflammation and tight junction protein in GI tissues (colon and ileum) and nervous tissues (amygdala and spinal cord) of animals with NP.
Methods: Twenty-eight male rats were randomly divided into 3 groups: sham control, spinal nerve ligation (SNL, pain model), SNL+0.375% (w/w in diet) GEG for 4 weeks. Pain sensitivity was assessed by von Frey filament tests, evoked audible vocalizations, and grimace tests in subjects. Intestinal permeability was assessed by lactulose/mannitol ratio in urine. The levels of mRNA expression of neuroinflammation (NF-κB and TNFα) in the colon and right amygdala were determined by qRT-PCR. Data were analyzed by mixed or one-way ANOVA followed by post-hoc Tukey's analysis.
Results: Compared to the sham group, the SNL group had significantly greater hypersensitivity (von Frey test), emotional responses (vocalizations), and spontaneous pain (grimace test). GEG supplementation significantly reduced hypersensitivity, emotional responses, and spontaneous pain (nose bulge, whisker change, and ear position) in SNL rats. GEG supplementation tended to decrease intestinal permeability of SNL-operated rats. The SNL group showed a significant increase in mRNA expression of TNFα in the colon and NF-kB in the right amygdala. GEG addition into the diet suppressed TNFα and NF-κB gene expression in the colon and the right amygdala. **Conclusions:** This study suggests GEG supplementation mitigated pain behaviors in a preclinical NP animal model. GEG also decreased SNL-induced neuroinflammation, intestinal permeability, and possible blood-brain barrier breakdown, which may explain the behavioral effects of GEG.
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BACKGROUND/OBJECTIVES

Emerging evidence suggests that the "leaky gut" may be linked to neuroinflammation, neuronal sensitization, and hyperexcitability in the development of neuropathic pain (NP). Targeting the leaky gut using bioactive compounds may represent a new therapeutic strategy to manage NP progression. Thus, this study examines the effect of dietary gingerol-enriched ginger (GEG) on pain sensitivity, intestinal permeability, and neuroinflammation-associated gene expression in brain and GI tissues of animals with NP.

HYPOTHESIS

GEG supplementation in diet would mitigate pain sensitivity, reduce intestinal permeability, and suppress neuroinflammation-associated gene expression in SNL-induced NP rats.

METHODS

Animals treatments: 28 male SD rats (5-week-old) for 3 groups:
Sham control, SNL, SNL+0.375% (w/w in diet) GEG for 4 weeks.
Pain sensitivity: assessed by von Frey filament test, evoked audible (20 Hz–16 kHz) and ultrasonic vocalizations (25 ± 4 kHz) with innocuous and noxious stimuli, and grimace tests.
Intestinal permeability: assessed by lactulose/mannitol ratio in urine
mRNA expression of TNF-α and NF-kB in colon and right amygdala by qRT-PCR.
Statistical analysis: mixed or one-way ANOVA followed by Tukey's post hoc analysis.

RESULTS

Figure 1. GEG supplementation mitigated NP hypersensitivity assessed by Von Frey test. Data are expressed as mean ±SEM, n=5-6/group. Data were analyzed by mixed ANOVA followed by a post hoc Tukey's test. *P < 0.05 vs Sham. ^{+}P < 0.05 vs SNL.

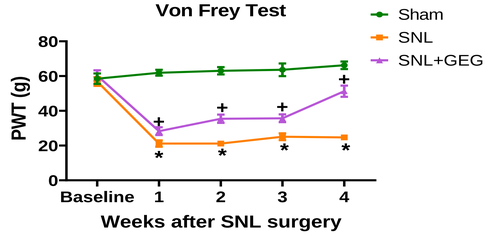

Figure 2. Effect of GEG supplementation on audible, pain-induced vocalizations in response to innocuous stimuli (left) and noxious stimuli (right). Data is expressed as mean ±SEM. n=5-6/group. Data were analyzed by one-way ANOVA followed by a *post hoc* Tukey's test. *P < 0.05. $^{\#}$0.05 < P <0.1.

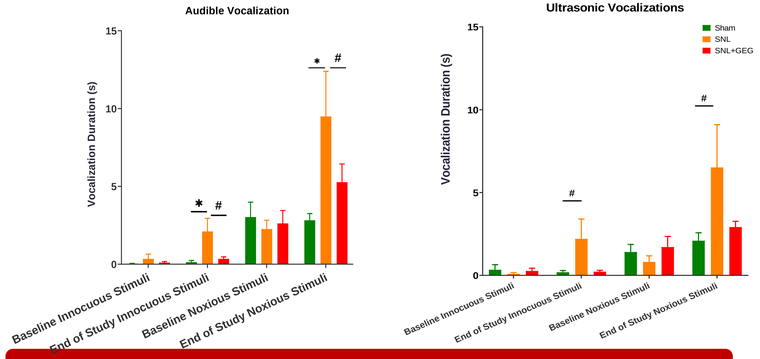

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Figure 3. GEG supplementation reduced NP-induced spontaneous pain behaviors assessed by Grimace test. Total score based on the following parameters: orbital tightening, ear position, whisker change, and nose bulge. Data are expressed as mean ±SEM (n=5-6/group) and data were analyzed by one-way ANOVA followed by a *post hoc* Tukey's test. *P < 0.05. $^{\#}$0.05 < P <0.1.

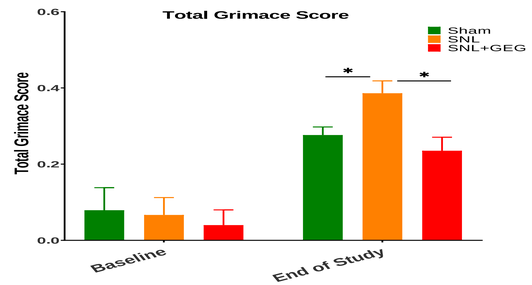


Figure 4. GEG supplementation improve intestinal integrity as shown by decreased ration of lactulose and D-mannitol (L/M) in the NP state. Data are expressed as mean ±SEM. Data were analyzed by one-way ANOVA followed by a *post hoc* Tukey's test. *P < 0.05. $^{\#}$0.05 < P <0.1.

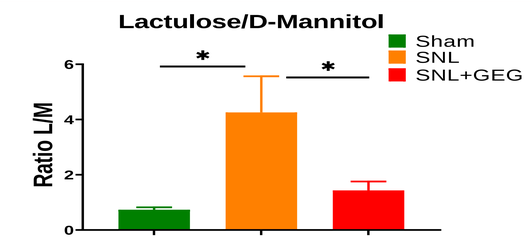
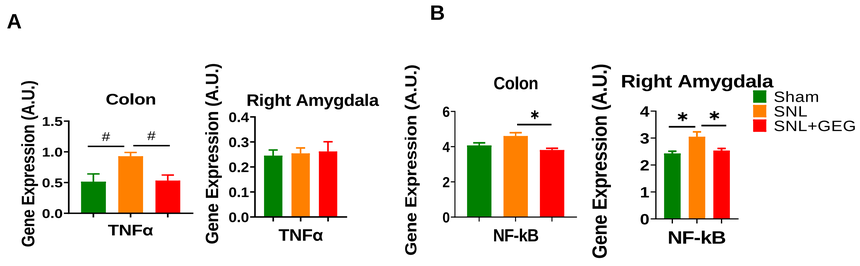


Figure 5. GEG supplementation suppressed mRNA expression in amygdala and colon in NP status. TNFα (A) and NF-kB (B). Data are expressed as mean ±SEM. n=5-6 per group. Data were analyzed by one-way ANOVA followed by a *post hoc* Tukey's test. *P < 0.05. $^{\#}$0.05 < P <0.1.



CONCLUSIONS

GEG minimized mechanical sensitivity and emotional responses associated with pain behavior as well as decreased spontaneous pain behavior (assessed by the Grimace test). Such pain-reduction effect maybe, in part, mediated via decreased intestinal permeability and neuroinflammation-associated gene expression, a gut-brain axis.