Anticonvulsant activity of some vanilloid receptor agonists
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ABSTRACT

Background: Vanilloid receptors 1 (VR 1), a group of transient receptor potential channels family was cloned in 1997. They were found to be a potential target for treatment of different acute and chronic pain disorder. Recently these receptors were reported to be involved in several pathological conditions.

Objectives: The present study aimed to investigate the potential anticonvulsant activity of five vanilloidal agonists (capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol).

Methods: Experimental animal model of pentylenetetrazole (PTZ) induced seizure was used to investigate the potential anticonvulsant activity of capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol.

Results: The data obtained showed that, all tested compounds (capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol) possess dose dependant anticonvulsant activity.

Conclusion: The five vanilloidal agonists; capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol exhibit anticonvulsant activity and may find clinical applications.

Key words: Anticonvulsant, vanilloid receptor agonists and pentylenetetrazole
Preparation of working solutions of chemicals:
Freshly prepared solutions of pentylentetrazole dissolved in normal saline, capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol dissolved in 5% tween were used.

Experimental animals:
Albino rats of both sexes weighing 150 – 200 g were used. The animals were kept and maintained under appropriate laboratory conditions, allowed free access to water and fasted for an over night before the experiment.

Assessment of anticonvulsant activity:
Pentylenetetrazole-induced seizure test:
The pentylenetetrazole induced seizure model was used to evaluate the anticonvulsant activity of some vanilloidal compounds (capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol). The test was carried out similar to that described by Swinyard and Kupferberg. For each compound, groups of rats of both sexes (n= 5) were used. Rat groups received the tested materials intraperitoneally. Thirty minutes later, rats were injected with pentylenetetrazole (90 mg/kg) subcutaneously. The animals were placed individually in an observation chamber and observed for induction of seizure within thirty minutes.

Figure 1: Vanilloidal compounds with the three main structural regions. A) Aromatic or vanillyl moiety; B) Polar portion of the side chain; C) Non polar portion of the side chain.
Table 1: Anti-pentylentetrazole activity of capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Seizure protection (%)</th>
<th>Mortality protection %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (negative control)</td>
<td>10 ml/kg</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Sodium valproate (positive control)</td>
<td>300 mg/kg</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Capsaicin</td>
<td>0.03 mg/kg</td>
<td>25</td>
<td>75</td>
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<td></td>
<td>0.06 mg/kg</td>
<td>50</td>
<td>100</td>
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<tr>
<td></td>
<td>0.3 mg/kg</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Nonivamide</td>
<td>0.035 mg/kg</td>
<td>50</td>
<td>50</td>
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<td></td>
<td>0.07 mg/kg</td>
<td>50</td>
<td>50</td>
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<tr>
<td></td>
<td>0.14 mg/kg</td>
<td>100</td>
<td>75</td>
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<tr>
<td></td>
<td>2 mg/kg</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Zingerone</td>
<td>0.125 mg/kg</td>
<td>50</td>
<td>50</td>
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<tr>
<td></td>
<td>1 mg/kg</td>
<td>75</td>
<td>75</td>
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<tr>
<td></td>
<td>5 mg/kg</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Dehydrozingerone</td>
<td>0.5 mg/kg</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg</td>
<td>50</td>
<td>50</td>
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<tr>
<td></td>
<td>2 mg/kg</td>
<td>75</td>
<td>75</td>
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<tr>
<td></td>
<td>5 mg/kg</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6-gingerol</td>
<td>4 mg/kg</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

A positive control was conducted on one group of rats (n=3), which received sodium valproate (300 mg/kg, i.p.). Fifteen minutes later rats were injected with pentylenetetrazole (90mg/kg s.c.) and observed for induction of seizures within thirty minutes. All the experimental groups were compared to the negative control group treated with vehicle (tween20 10 ml/kg). The percentage of mortality protection was also recorded during 24 hours.

Results:
Anticonvulsant activity:
Capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol, were investigated for their potential anticonvulsant activity. A dose dependant anti-PTZ activity was produced by all tested vanilloid compounds (table 1).

Capsaicin (0.3 mg/kg), nonivamide (0.14 mg/kg), zingerone (5 mg/kg), dehydrozingerone (5mg/kg) and 6-gingerol (4mg/kg) produced 100% anti-PTZ activity. Compared to the negative control, all doses tested for the five compounds showed considerable mortality protection.

Discussion:
The present study showed and for the first time to our knowledge that the five tested vaniloiald agonists; capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol could have potential anticonvulsant activity especially for absence seizures. Literature showed no reported data about anticonvulsant activity of these compounds. In addition, they reduce the toxicity of pentylenetetrazole since they showed considerable mortality protection.
Capsaicin, the prototype VR1 ligand has been structurally divided into three regions \(^{13, 15-18}\). Region A represents the vanillyl aromatic part, region B represents the polar part of the side chain and region C represents the non-polar; hydrophobic part of the side chain (Fig.1). All previous studies agreed on the importance of vanillyl aromatic part in the vanilloid agonistic activity. Capsaicin showed anticonvulsant activity at lower doses compared to the other four vanilloid compounds tested. This result is in accordance with that found by Vadim et al who reported that vanilloid receptors agonistic activity (efficacy) is hydrophobic dependent\(^{19}\). Moreover, the hydrophobic side chain appears to be essential for drug binding with the vanilloid receptor carbon chain site\(^{20}\), a property that could facilitate the design of vanilloid agonists and to measure their toxicity profiles.

**Conclusion:**
The present study confirms that capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol possessed potential anticonvulsant activity against pentylenetetrazole induced seizure. Therefore, they could be potential anticonvulsant agents and/or Co-drugs in combination with antiepileptic drugs, especially if further investigations are conducted clinically to explore their possible efficacious use.

**References:**
17. Walpole CSJ, Wrigglesworth R, Bevan S, Campbell EA, Dray A, James IF, Perkins MN, Reid DJ and Winter J. Analogues of capsaicin with


