Original Article

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

Vanilloid receptors 1 (VR1), belong to the transient receptor potential (TRP) channels family. They were cloned in 1997[1]. VR1 are considered to be integrators of noxious chemical and physical stimuli that can be activated by capsaicin, heat and low pH[2,3]. There are numerous published studies confirm that these receptors have a role in transduction and modulation of acute and chronic pain. Based on these studies they were found to be a potential target for treatment of different acute and chronic pain disorders[4]. Recently these receptors were reported to be involved in several pathological conditions. Previous studies reported that, there is an increase expression of VR1 in tissues obtained from patients affected by many pathological conditions, such as inflammatory bowel disease, oesophagitis, rectal hypersensitivity, vulvodynia, prurigo nodularis and cervical carcinoma[5-10]. Selective ligands or modulators of these channels are substances of potential interest to treat such diseases[11,12]. Natural products seem to be interesting sources of compounds that might be prototype VR1 ligands[1]. Capsaicin, the prototype VR1 ligand increase the release of the intracellular calcium which triggers the release of neuropeptides such as substance P and the calcium gene-related peptide CGRP[13]. Many other naturally occurring vanilloid receptor-1 agonists were detected such as gingerols, shogaols, paradols, zingerone, piperine and eugenol[1].

The present study aimed to investigate the anticonvulsant activity of somevanilloid receptor-1 agonists as capsaicin, nonivamide (capsaicin analogue), zingerone, dehydrozingerone and 6-gingerol in experimental animal models.

Materials and methods:

Chemicals:

Pentylentetrazole, capsaicin, nonivamide, zingerone, dehydrozingerone, 6-gingerol and tween$_{20}$.

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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$_{20}$ 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[14]. 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.

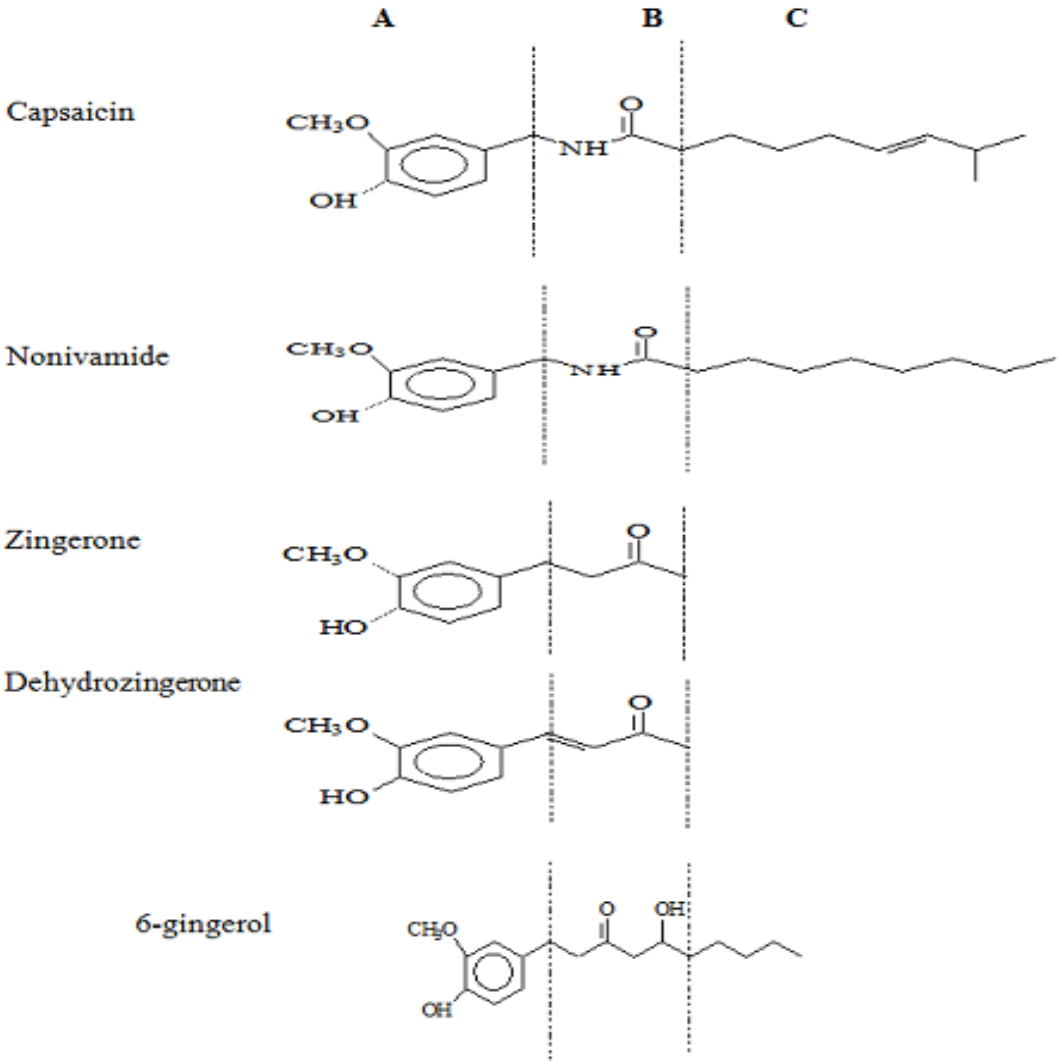

Figure 1: Vanilloidal compounds with the three main structural regions. A) Aromatic or vanillyl moiety; B) Polar portion of the side chain; C) Non polar portion of the side chain.

Table 1: Anti-pentylentetrazole activity of capsaicin, nonivamide, zingerone, dehydrozingerone and 6-gingerol.

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

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 ($tween_{20}$ 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 vaniloidal 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.

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