



INHIBITORY EFFECT OF EPINEPHRINE AND NOREPINEPHRINE ON CARRAGEENIN-INDUCED PLANTAR EDEMA IN THE RAT

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In this short paper we report that carrageenin-induced plantar edema in the rat paw is inhibited by epinephrine or norepinephrine. When these catecholamines are administered in combination with carrageenin, they inhibit the inflammatory response in the following three hours, at which point the effects gradually subside.

KEYWORDS: *carrageenin, epinephrine, norepinephrine, edema, inflammation, catecholamines*

Inflammation is a typical immune mechanism, which is established in the presence of chemical, physical, or biological pathogens with tissue and vascular damage, but also some self-type of immune reactions can cause inflammation and cell death (1). Irritating foreign substances injected into tissue can cause inflammation and edema (2). Carrageenin is a complex molecule extracted from red algae (*Chondrus crispus* and *Gigartina stellata*) which contains two polysaccharides (3). When carrageenin is injected into the plantar rat paw, it causes an increase in the levels of fatty acids, including hydroxyeicosatetraenoic acid (5-HETE), which mediates inflammation (4). Tissue edema is a clinical manifestation with abnormal accumulation of lymphatic fluid at the inflamed site, characterized by swelling, reduced function, and often pain (5).

Catecholamines are water-soluble chemical compounds (hormones) released by the adrenal glands under conditions of stress, that circulate in the blood bound to plasma proteins (6). The most well-studied catecholamines are epinephrine (adrenaline) and norepinephrine (noradrenaline) which derive from dopamine, which in turn derives from tyrosine (7) (Fig. 1).

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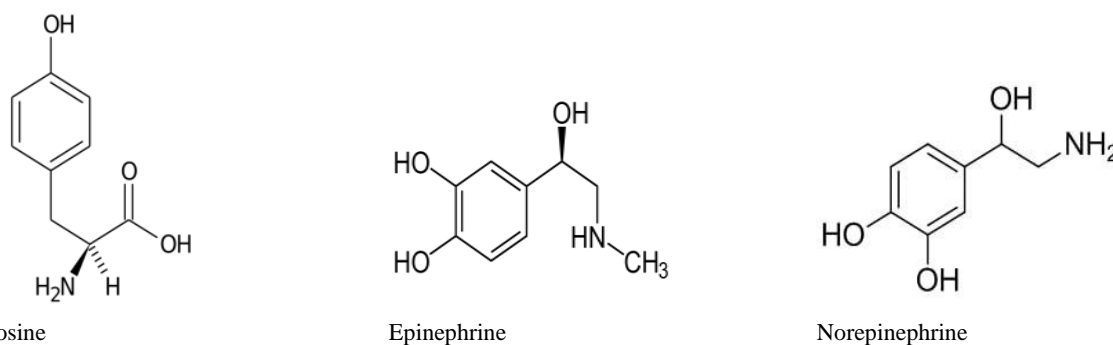


Fig. 1.

Epinephrine and norepinephrine, secreted by the adrenal gland and local sympathetic neurons, regulate the immune system by activating the β 2-adrenergic receptor on immune cells, producing cell migration and cytokine secretion (Adrenergic regulation of immune cell function and inflammation (8)). The aim of this study is to investigate whether these two catecholamines inhibit carrageenin-induced inflammation.

In this study, carrageenin is injected alone intraplantar and in combination with the epinephrine or norepinephrine in order to inhibit plantar edema (9). Male Wistar rats (100-180 g) were used and anti-edematous activity of epinephrine and norepinephrine by simultaneous injection with carrageenin was investigated and after 3 h the edema was measured. Paw edema was induced by intraplantar injection of 0.1 ml of 1% solution of carrageenin. The volume was measured in a nanogram of the rat paw.

Using this experimental model, we report the inhibitory action of epinephrine and norepinephrine on carrageenin-induced plantar edema in rats. The inhibitory action of these two catecholamines is short-lived, starting immediately after injection and reaching the plateau at 3 h after treatment, an effect that gradually decreased. The efficacy of epinephrine and norepinephrine is high except for dopamine, for which higher doses are needed (data not shown). The inhibitory effect of norepinephrine was slightly less pronounced than that of epinephrine.

The results obtained demonstrate that carrageenin causes a strong inflammatory effect (Table I) correlating to the amount of edema on the sole of the rat's foot (10). When epinephrine and norepinephrine are administered with carrageenin, the inflammatory effect is strongly inhibited. This inhibition appeared only for a short period of time (3 h) and then gradually decreased over time.

Table I. Experiment performed three times in triplicate.

Treatment	ng/paw	nmol/paw
Carrageenin 1mg (0.1 ml of 1% solution)	450 (+/- 90)	2.35
Carrageenin 1mg (saline solution)	430 (+/- 70)	2.01
Carrageenin + Epinephrine 10^{-7} M	44 (+/- 12)	0.13
Carrageenin + Norepinephrine 10^{-7} M	75 (+/- 27)	0.44

In this table we show that carrageenin causes severe edema in the plantar of the rat paw and when it is given in combination with epinephrine or norepinephrine, strong inhibition is obtained for 3 hours.

DISCUSSION

Epinephrine and norepinephrine are endogenous anti-inflammatory catecholamines which are released after an inflammatory process as a defensive response of the body to try to restore the physiological tissue state (11).

In this short article, the powerful inflammatory effect of carrageenin is confirmed, and we demonstrate that when this proinflammatory compound is administered in combination with epinephrine or norepinephrine, inflammation is inhibited in the first phase of induction, an effect that diminishes over time until it disappears (12). In addition, in our experiments, epinephrine and norepinephrine were increased in the urine of the rats treated with carrageenin induced edema, an effect that may be species specific and thus not detectable in humans (13). It has been reported that in humans, inflammatory stimuli such as ultraviolet radiation causes a decrease in epinephrine or norepinephrine (Nicotinic acetylcholine receptors in glucose homeostasis: the acute hyperglycemic and chronic insulin-sensitive effects of nicotine suggest dual opposing roles of the receptors in male mice (14, 15).

In conclusion, epinephrine or norepinephrine can inhibit the edematous inflammatory response of carrageenin in the first 3 hours after the combined treatment, followed by a gradual decrease in inhibition until it disappears (16).

Conflict of interest

The author declares that they have no conflict of interest.

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