

NITROGEN MONOXIDE PRODUCTION SUPPRESSOR

FIELD OF THE INVENTION

The present invention relates to a novel pharmacological action of an extract from inflammatory tissue inoculated with vaccinia virus. More particularly, it relates to a pharmaceutical agent such as a nitrogen monoxide production suppressor, a therapeutic agent for sepsis, an antiendotoxin agent and a therapeutic agent for endotoxin shock containing the extract from inflammatory tissue inoculated with vaccinia virus as an effective component.

BACKGROUND OF THE INVENTION

It has been known that, against the outside invasion by virus, etc. and against the progression of inner diseases, the living body produces various biofunction-regulating substances for maintaining its homeostasis and for regulating and normalizing the biofunctions. Two phases are involved consisting of a suppressing action to excessive reactions, and an enhancing action to depression of functions. For example, there have been various reports on biofunction-regulating substances which are produced in inflammatory tissue inoculated with vaccinia virus, methods for extracting said substances from diseased tissues, and pharmacological activities thereof, as disclosed, for example, in Japanese Examined Patent Publications Sho-63/039,572 B, published Aug. 5, 1988, Sho-63/025,600 B, published May 26, 1988, and Hei-03/043,279 B, published Jul. 1, 1991, and U.S. Pat. No. 5,013,558 to Konishi.

A commercially available drug preparation of an extract from inflammatory rabbit skin inoculated with vaccinia virus is sold in Japan under the trade name Neurotropin by Nippon Zoki Pharmaceutical Co., Osaka, Japan. As mentioned at page 1,434 of "Drugs in Japan, Ethical Drugs" (published in August of 1994; edited by Japan Pharmaceutical Information Center; published by Yakugyo Jihō Co., Ltd.), this preparation is a drug containing a non-protein active substance extracted and isolated from inflammatory tissues of rabbits inoculated with vaccinia virus. The preparation has been allowed for treatment of lower back pain, neck-shoulder-arm syndromes, peri-arthritis scapulohumeralis, osteoarthritis, symptomatic neuralgia, itching accompanied with skin disorders (such as eczema, dermatitis and urticaria), allergic rhinitis, sequelae of subacute myelo-optico-neuropathy (such as coldness, pain and paresthesia/dysesthesia), etc. It is approved as an ethical drug in the form of injections (subcutaneous, intramuscular and intravenous) and tablets, and is commercially available.

Neurotropin was used in an experimental study at the School of Medicine, University of California, Davis, to evaluate its influence on thymic microenvironmental abnormalities of New England black mice as reported by Y. Takeoka et al, *Int. J. Immunotherapy*, XI(2), pp. 49-56 (1995). As taught by Takeoka et al, Neurotropin is a non-protein extract isolated from the inflamed dermis of rabbits inoculated with vaccinia virus and it has been reported in the literature as: 1) having beneficial effects on immune-depressed animals, 2) clinically useful as an analgesic and as an anti-allergy drug with few side-effects in humans, 3) improving the immune status of murine lupus in (NZB/NZW) F1 mice, and 4) inhibiting the development of EAE in Lewis rats, an autoimmune model of human multiple sclerosis.

As mentioned above, it is known that an extract from inflammatory tissue inoculated with vaccinia virus has vari-

ous pharmacological actions such as analgesic action, sedative action, antiallergic action and action of improving peripheral circulation, as disclosed in Japanese Examined Patent Publications Sho-63/039,572 B, Sho63/025,600 B and Hei-03/043,279 B. However, there has been no report at all concerning the novel pharmacological actions of the present invention such as a suppressing action to nitrogen monoxide production, a therapeutic action for sepsis, an antiendotoxin action, and a therapeutic action for endotoxin shock.

In sepsis and other serious bacterial infectious diseases, endotoxin (an intracellular toxin) is produced and, as a result of its action, shock symptoms occur. Endotoxin shows a variety of actions toward a living organism such as fever, leukocytosis, activation of complement and the kinin system, induction of disseminated intravascular coagulation syndrome (DIC), and suppression of bone marrow. When the shock symptoms from endotoxin progresses, an excessive hypotension, reduction of cardiac output, little urinary excretion, disturbance of consciousness, etc. are induced whereby the living body enters a very serious state. It has been suggested that a rapid hypotension upon endotoxin shock is due to excessive nitrogen monoxide which is abnormally produced by the action of endotoxin upon the vascular endothelial cells. There have been investigations on inhibitors for nitrogen monoxide synthesizing enzymes such as arginine derivatives with an object of achieving therapeutic agents for treating the hypotension resulting from the endotoxin shock.

The present inventors have conducted various tests and studies on pharmacological activity of an extract from inflammatory tissue inoculated with vaccinia virus and, as a result, they have found that said extract suppresses death of cells and excessive production of nitrogen monoxide induced by endotoxin. The extract also has an improving action toward hypotension induced by endotoxin whereupon the present invention has been achieved.

The present invention provides a pharmaceutical composition containing an extract from inflammatory tissue inoculated with vaccinia virus for use as a nitrogen monoxide production suppressor, a therapeutic agent for sepsis, an antiendotoxin agent and a therapeutic agent for endotoxin shock.

SUMMARY OF THE INVENTION

The production of nitrogen monoxide and nitrogen monoxide synthetase caused by endotoxin is suppressed by an extract from inflammatory tissue inoculated with vaccinia virus. The extract may be used for treating or preventing a disease or condition in which abnormal levels of nitrogen monoxide are produced, such as hypotension induced by endotoxin. Serious bacterial diseases in which endotoxin is produced, such as sepsis, as well as endotoxic shock, may be treated or prevented by administering to a patient in need of such treatment or prevention a pharmaceutically effective amount of the extract from inflammatory tissue inoculated with vaccinia virus. In embodiments of the invention, the inflamed tissue may be human or animal tissue, such as tissue of a mammal, for example skin tissue of a rabbit or other mammal. Administration of the extract may, for example, be orally or by injection.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the inhibitory effect of the substance of the present invention upon the death of endothelial cells caused by LPS.