PREVENTION OF RESPIRATORY INFECTIONS IN FOWL

BACKGROUND OF THE INVENTION

Domestic and captured birds as well as wild birds are susceptible to influenza type A virus infections. These viruses are highly pathogenic and can cause mortality up to 100 % in domestic flocks. Avian paramyxoviruses cause diseases such as Newcastle disease (ND) which can have severe negative effects on domestic flocks. Other respiratory viruses affecting fowl include infectious bronchitis virus and avian pneumovirus. While these effects are felt economically by producers and consumers, they also present public health issues. Birds are thought to provide a reservoir for viruses that infect human populations.

There is a continuing need in the art for means of controlling respiratory viral infections in bird populations.

SUMMARY OF THE INVENTION

According to one embodiment of the invention a method is provided for preventing respiratory viral infections in domestic fowl. An effective amount of an agent in admixture with feed is administered to domestic fowl. The agent is selected from the group consisting of: substance P, [Met-OH^{11}]-substance P, [Met-OMe^{11}]-substance P, [Nle^{11}]-substance P, [Pro^{9}]-substance P, [Sar^{9}]-substance P, [Tyr^{8}]-substance P, Sar^{9}, Met (0_2) 11-Substance P, and [p-Cl-Phe^{7,8}]-substance P. The infection rate is decreased by means of the administration.

According to another aspect of the invention another method is provided for preventing respiratory viral infections in domestic fowl. An effective amount of an agent in an aerosol is administered to domestic fowl. The agent is selected from the group consisting of: substance P, [Met-OH^{11}]-substance P, [Met-OMe^{11}]-substance P, [Nle^{11}]-substance P, [Pro^{9}]-substance P, [Sar^{9}]-substance P, [Tyr^{8}]-substance P, Sar^{9}, Met (0_2) 11-Substance P, and [p-Cl-Phe^{7,8}]-substance P. The rate of infection is decreased by the administration.

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DETAILED DESCRIPTION OF THE INVENTION

It is a discovery of the present inventor that Substance P and its bioactive analogs, such as Sar^{9}, Met (0_2) 11-Substance P, are beneficial preventatives against respiratory virus infections in domestic fowl. Substance P and its analogs potentiate the lung's immune response against respiratory viruses. Substance P and its analogs can be used to prophylactically treat poultry to minimize infection and to minimize spread of infection between birds and to other species, including humans.

Substance P (RPKPQQFFGLM-NH_2; SEQ ID NO: 1) or a bioactive analog thereof such as Sar^9, Met (0_2) 11-Substance P can be administered to prevent or treat respiratory virus infections. The bioactive analog can be selected from the group consisting of [Met-OH^{11}]-substance P, [Met-OMe^{11}]-substance P, [Nle^{11}]-substance P, [Pro^9]-substance P, [Sar^9]-substance P, [Tyr^8]-substance P, Sar^9, Met (0_2) 11-Substance P, and [p-Cl-$Phe^{7,8}$]-substance P. Other compounds which function in the same way can be identified by their ability to compete with substance P for binding to its receptor (NK-1) or for their ability to agonize the NK-1 receptor. Routine assays for such activities are known in the art and can be used.

The substance P or analog can be administered by any method known in the art, including via aerosol inhalation and via admixture with feed. Intravenous, intratracheal, intrabronchial, intramuscular, sublingual, and oral administrations can also be used. Preferred dosages include 0.05 to 5 nanomolar substance P or analog for intravenous administration, preferably 0.1 to 2 nanomolar, and more preferably 0.5 to 1.5 nanomolar. For aerosol administration dosages include 0.05 to 75 micromolar substance P or analog, preferably 0.1 to 2 micromolar, and more preferably 0.5 to 1.5 micromolar. Typical concentration ranges of substance P or its bioactive analog in the aerosol administered is between 0.001 and 10 μM. It can be advantageously administered as a liquid at a concentration between about 0.1 and 10 μM.

Bioactive analogs, according to the invention are those which act as competitive inhibitors of SP by binding to the SP receptor (NK-1 receptor). The analogs may be agonists of the NK-1 receptor. Other derivatives as are known in the art and commercially available (*e.g.*, from Sigma) can be used. In addition, substance P fragments and derivatized substance P fragments may also be used. Substitution, deletion, or insertion of one to eight amino acid residues, and preferably from one to

three amino acid residues, will lead to analogs which can be routinely tested for biological activity. In addition, functional groups may be modified on SP while retaining the same amino acid backbone. Again, routine testing will determine which of such modifications do not adversely affect biological activity.

Suitable devices for administering the aerosol of the present invention include nebulizers as well as hand-held aerosol "puffer" devices. Suitable treatment regimens for treatment according to the present invention include one-time, monthly, weekly, daily or multiple daily treatment by aerosol. Frequency may depend on the immediate risk of infection in a geographical area at a particular time. Other modes of treatment include continual transdermal infusion; intravenous, intramuscular, sublingual, and subcutaneous injections; and oral administration. Suitable formulations of substance P for administration are any which are veterinarially acceptable and in which the substance P or bioactive analog retains its biological activity. Generally, such formulations are substance P dissolved in normal saline, which is optionally sterile. Other formulations for changing absorption and half-life characteristics can be used, including liposomal formulations and slow-release formulations.

Disease features of respiratory viral infections include Clara cell necrosis, increased pulmonary alveolar macrophage number, neutrophil number, alveolar-capillary barrier membrane damage, surfactant depletion, and increased 6-keto-$PGF_{1\alpha}$ and PGE_2 concentrations. These disease features are reduced in a population by the prophylactic administrations of the present invention. Decreases in the disease features or rates of infection in a population of at least 10 %, 15 %, 20 %, 25%, 30 %, 35 %, 40 %, or 50 % are desirable. Even greater decreases are preferred.

I/WE CLAIM:

1. Use of substance P or substance P analog for the manufacture of a medicament for preventing viral infections in domestic fowl comprising: administering to domestic fowl an effective amount of a medicament in admixture with feed, said substance P or substance P analog selected from the group consisting of: substance P, [Met-OH^{11}]-substance P, [Met-OMe^{11}]-substance P, [Nle^{11}]-substance P, [Pro^{9}]-substance P, [Sar^{9}]-substance P, [Tyr^{8}]-substance P, [Sar^{9}, Met $(0_2)^{11}$]-substance P, and [p-Cl-$Phe^{7,8}$]-substance P, whereby infection rate is decreased.

2. Use of substance P or substance P analog for the manufacture of a medicament for preventing respiratory viral infections in domestic fowl comprising:

   administering to domestic fowl an effective amount of a medicament in an aerosol, said substance P or substance P analog selected from the group consisting of: substance P, [Met-OH^{11}]-substance P, [Met-OMe^{11}]-substance P, [Nle^{11}]-substance P, [Pro^{9}]-substance P, [Sar^{9}]-substance P, [Tyr^{8}]-substance P, [Sar^{9}, Met $(0_2)^{11}$]-substance P, and [p-C1-$Phe^{7,8}$]-substance P.

3. Use of substance P or substance P analog for the manufacture of a medicament for preventing respiratory viral infections in domestic fowl comprising:

   administering to domestic an effective amount of a medicament, wherein said administration is intramuscular, intravenous, intrabronchial, sublingual, intratracheal or subcutaneous, and wherein said substance P or substance P analog is selected from the group consisting of: substance P, [Met-OH^{11}]-substance P, [Met-OMe^{11}]-substance P, [Nle^{11}]-substance P, [Pro^{9}]-substance P, [Sar^{9}]-substance P, [Tyr^{8}]-substance P, [Sar^{9}, Met $(0_2)^{11}$]-substance P, and [p-Cl-$Phe^{7,8}$]-substance P.

4. The method of claim 1, 2, or 3 wherein the domestic fowl is a chicken.

5. The method of claim 1, 2, or 3 wherein the domestic fowl is a turkey.

6. The method of claim 1, 2 or 3 wherein the domestic fowl is a duck.

7. The method of claim 1, 2 or 3 wherein the domestic fowl is a goose.

8. The method of claim 1, 2, or 3 wherein [Sar^{9}, Met $(0_2)^{11}$]-Substance P is administered.

9. The method of claim 1, 2, or 3 wherein substance P is administered.

10. The method of claim 1, 2, or 3 wherein [$Met\text{-}OH^{11}$]-substance P is administered.

11. The method of claim 1, 2, or 3 wherein [$Met\text{-}OMe^{11}$]-substance P is administered.

12. The method of claim 1, 2, or 3 wherein [Nle^{11}]-substance P is administered.

13. The method of claim 1, 2, or 3 wherein [Pro^{9}]-substance P is administered.

14. The method of claim 1, 2, or 3 wherein [Sar^{9}]-substance P is administered.

15. The method of claim 1, 2, or 3 wherein [Tyr^{8}]-substance P is administered.

16. The method of claim 1, 2, or 3 wherein [$p\text{-}Cl\text{-}Phe^{7,8}$]-substance P is administered