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INVESTIGATION OF THE ANTIVIRAL AND INTERFEROGENIC ACTIVITY OF SOME VINYL PYRROLIDONE COPOLYMERS

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# INVESTIGATION OF THE ANTIVIRAL AND INTERFEROGENIC ACTIVITY OF SOME VINYL PYRROLIDONE COPOLYMERS

by

N. A. Zeytlenok, L. M. Vyulner, and
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# INVESTIGATION OF THE ANTIVIRAL AND INTERFEROGENIC ACTIVITY OF SOME VINYL PYRROLIDONE COPOLYMERS

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Many nonviral agents are capable of forming interferon in animal organisms: ricketsia [11], bacteria [3, 20], protozoa [9, 16], extracts from bacteria [5, 7, 10, 18, 21], fungi [13, 17], plants [19], nucleic acids from foreign cells [12], etc. However, it is impossible to use many of these interferogens in medical practice due to their pathogenic nature or their toxicity in effective concentrations. Also, many of these interferogens are almost inactive or have antigenic properties, which hinders or limits their application. This indicates the expediency of seeking better interferogens.

Kleinschmidt et al. suggested in 1964 [13] that the interferogenic activity of statolone and other interferon inducers results from their polyanionic structure. If this is so, the search for active interferogens among nontoxic synthetic compounds with polyanionic structure is justified. The absence of infectious and antigenic properties in these materials, the possibility of industrial production of these materials in large quantities are advantages to be expected from synthetic interferogens over those produced biologically. In connection with this, we began a study of the antiviral and interferogenic activity of certain synthetic high- and low-molecular compounds in 1966 [4, 6].

In this report, we present the results of further study of the antiviral and interferogenic properties of a number of copolymers based on vinyl pyrrolidone, synthesized at the Institute of High Molecular Compounds, Academy of Sciences USSR.

## Materials and Methods

In our work we used the Absettarov strain of tick-borne encephalitis virus (VKE), the Smitsbury strain of Semliki forest virus (VLS) and the Indiana strain of the vesicular stomatitis virus (VVS). The sources of the first two viruses were 20-50% suspensions of brain tissue of infected mice, the source of the VVS was the encephalitic fluid of infected chick embryos. All viruses were stored at -20°. Three-day cultures of mouse fibroblasts were produced by trypsinization of the mouse embryos using the ordinary method and placement of 6-8 × $10^5$ cells in 1 ml of medium No. 199 with the addition of 5% native bovine serum. The vinyl pyrrolidone-based copolymers (VP polymers) were used in the form of 0.2-5% solutions in distilled water, pH 7.0.

Table 1. Characteristics of Vinyl Pyrrolidone -Based Copolymers

| Preparation No. | Second monomer in copolymers | Weight content of second monomer (%) | Molecular weight | Toxicity for mice (in mg/kg | |
|---|---|---|---|---|---|
| | | | | Introduced to peritoneal cavity | Maximum tolerable dose[1] |
| 20 | Crotonic acid | 14,9 | 60 000 | ≥6700 | 2500 |
| 44 | | 17,0 | 120 000 | — | |
| 50 | | 8,9 | 220 000 | — | |
| 46 | | 7,8 | 300 000 | — | 1400 |
| 28 | | 14,2 | 50 000 | ≥4500 | 2500 |
| 71 | Crotonaldehyde | 11,0 | 20 000 | — | — |
| 72 | | 5,0 | 45 000 | — | — |
| 73 | | 8,5 | 9 000 | ≥6600 | 2500 |
| 102 | | 4,8 | 30 000 | — | — |
| 103 | | 4,8 | 30 000 | ≥7000 | ≥5000 |
| 74 | | 7,0 | 60 000 | — | — |
| 106 | | 5,8 | 60 000 | ≥7000 | ≥5000 |
| 2 | Maleic acid | 7,0 | 500 000 | — | — |
| 11 | | 6,8 | 700 000 | ≥6700 | 1250 |
| 11—П/1282 | Vinylamine | 6,4 | 29 500 | 56 | 25 |
| 10 | Vinyl pyrrolidone homopolymer | 0 | 200 000 | — | 5000 |

Note. [1] Maximum tolerable dose determined from 100% survival of animals

-- Means not studied.

From the data shown in Table 1 we can see that the second monomer in the copolymers was crotonic acid, crotonaldehyde, maleic anhydride, vinylamine, etc. The molecular weights and relative quantities of the second monomer were various, even in copolymers with the same second monomer.

The antiviral activity of the copolymers was studied in experiments using BALB mice, with the copolymer solutions introduced intraperitoneally. The toxicity of each group of preparations was first studied for mice with intraperitoneal injection (see Table 1). The infection was performed with a ten-times dilution of VKE or VLS subcutaneously 3-24 hr after introduction of the preparations. Eight to ten mice were taken for each dilution of the virus. In the individual experiments, infection was performed with only one virus dose (50-100 $LD_{50}$). The effectiveness of the preparations was determined by the logarithms of resistance indices (IR) defined as the difference in the logarithms of the virus titre in the control and in the experimental groups. When a large group of mice was infected by one virus dose, the criterion of effectiveness of the preparations was the difference in the percentages of survival of the control and experimental animals.

Also, in some experiments the level of multiplication of the virus in the blood and brain of the mice on the third to fifth day after their infection with a relatively low dosage of the virus (50-100 $LD_{50}$) was determined. In these cases, the concentration of virus was established from the results of titration of suspensions of heparinated blood or brain tissue of the mice in medium No. 199 in experiments on mice weighing 7-8 g, infected intracerebrally. The difference in the virus titre in the experimental and control groups expressed as a logarithm is the index of suppression of multiplication of the virus (IP), which was used as the indicator of effectiveness of the preparations.

The interferonogenic activity of the copolymers was studied in experiments on mice weighing 16-20 g, which had received 0.5 ml of the preparate solution intraperitoneally. Blood was taken from the mice after various time intervals, the serum was produced, then the interferon content was measured. The activity of the interferon was determined in a culture of mouse embryo cells by establishment of 50% platelet formation of the suppressing dose ($PID_{50}$/ml) in the ratio 50-100 BOE VVS.

## Conclusions

Table 2 shows the results of tests of a number of copolymers with the experimental tick-borne mouse encephalitis. The copolymers were

introduced to mice three hours before infection intraperitoneally in quantities of 300-600 mg/kg. As we can see from Table 2, the IR of the animals who received various copolymers of VP with crotonic acid, crotonaldehyde or maleic anhydride were generally low, and in many cases unreliable. The decrease in lethality of the mice infected with small virus doses is not great here due to the usage of insufficiently large groups of animals. However, when infected with small doses of the virus, some of these preparations resulted in an essential inhibition of accumulation of virus in the blood and brain, by 2-3 orders of magnitude. This indicates a certain degree of antiviral activity of these copolymers.

Table 2. Antiviral Activity of Polyvinyl Pyrrolidone and Vinyl Pyrrolidone-Based Polymers with Experimental Tick-Borne Encephalitis of Mice

| Preparate No. | Second component in copolymer | Dose (mg/kg) | Increase in resistance of mice (log IR) | Reduction of virus titre in organism of mice (in log IP) | |
|---|---|---|---|---|---|
| | | | | Blood | Brain |
| 20 | Crotonic acid | 300 | 1,0 | 1,75 | 2,5 |
| 28 | | 300 | 1,0 | — | — |
| 44 | | 300 | 0,6 | 0,3 | 2,2 |
| 46 | | 300 | 0,8 | 1,0 | 2,0 |
| 50 | | 300 | 0 | — | 1,75 |
| 71 | Crotonaldehyde | 400 | 1,3 | 2,0 | 3,0 |
| 72 | | 400 | 0,1 | — | — |
| 73 | | 600 | 1,1 | 2,25 | 3,5 |
| 74 | | 600 | 1,7 | — | — |
| 102 | | 400 | 1,0 | 0 | 0 |
| 103 | | 400 | 1,0 | 0 | 0 |
| 106 | | 400 | 1,0 | — | — |
| 2 | Maleic anhydride | 300 | 1,8 | 2,2 | 3,0 |
| 11 | | 300 | 1,6 | — | — |
| 10 | None | 600 | 1,7 | 2,3 | 3,3 |

Note. Preparates injected into mice 3 hr before injection
-- Means no investigation performed

Table 3 shows the results of two typical series of experiments, in which small doses of VKE were used with rather large numbers of mice. In these experiments, the antiviral activity of the copolymers which varied in composition, molecular weight and electrical charge was even more clearly expressed. 40-70% of the mice survived if they were preliminarily given VP copolymers intraperitoneally with crotonic acid, maleic anhydride or crotonaldehyde at 400 mg/kg. Only 14% of the mice

in the control group survived. The differences are clear and statistically reliable ($P < 0.01$). The results of other experiments were similar.

According to the data of Table 4, copolymers at a dosage of 250 mg/kg in the experiments on mice had an antiviral effect only if injected prophylactically before contamination with VLS (log IR-2.9). If the preparation was introduced 24 or 48 hr after infection, no protective effect was observed.

Table 3. Influence of Vinyl Pyrrolidone-Based Copolymers on Lethality of Mice Infected in the Brain with Tick-Borne Encephalitis Virus (50-100 $LD_{50}$)

| Series of experiments | Preparate No. | Second component in copolymer | Molecular Weight | Charged | No. of mice | |
|---|---|---|---|---|---|---|
| | | | | | Survived | |
| | | | | | abs | % |
| I | 20<br>74<br>— | Crotonic acid<br>Maleic anhydride<br>Crotonaldehyde<br>Control (nutrient medium | 60 000<br>150 000<br>50 000 | 77<br>78<br>75<br>76 | 54<br>54<br>30<br>11 | [illegible]<br>[illegible]<br>40 ± 4,1<br>11 ± 3,0 |
| II | 71<br>— | Crotonaldehyde<br>Control (nutrient medium) | 18 000 | 100<br>100 | 57<br>21 | 57±4,9<br>21±4,1 |

Copolymers at 400 mg/kg in 0.5 ml introduced to peritoneal cavity 2 hr before inoculation of virus

It should be noted that the antiviral effect of the copolymer is essentially influenced by the age of the mice. When the VP copolymer is introduced with crotonic acid, the values of log IR for Semliki forest virus in mice weighing 13-14 g and 7-8 g were 3 and 0.8 respectively. Similar results were produced with mice of differing ages treated with other copolymers and infected with VKE (log IR 1.5 and 0.25 respectively). Consequently, the preparations had a protective effect from viral infection of mice only for older animals (Table 5).

The antiviral activity of the copolymers was seen not only in the higher survival rate, but also in the delay of time of death of infected mice and was most clearly expressed in the first days after the beginning of death of the control animals. In connection with this, those mice who received VP copolymers with vinylamine or crotonic acid showed IR considerably higher, considering the death of the animals on the fifth day after infection, although the values were decreased gradually after the fifteenth day (Table 6).

Table 4. Influence of Time of Introduction of Vinyl Pyrrolidone Copolymer with crotonic Acid on Antiviral Activity

| Preparation No. | Time of introduction in relation to moment of infection with virus | Titres of Semliki forest virus (log $LD_{50}$/ml) | Protective effect (log IR) |
|---|---|---|---|
| Copolymer No. 28 | 2 hr before infection | 6,9 | 2,9 |
| Copolymer No. 28 | 24 hr after | 8,9 | —0,1 |
| Copolymer No. 28 | 48 hr after | 8,6 | 0,2 |
| Control (still water) | 2 hr before infection | 8,8 | — |

Note. The copolymer, dosage 250 mg/kg in 0.5 ml, introduced intraperitoneally for mice weighing 18-20 g. Semliki forest virus introduced subcutaneously, 8 mice per dilution.

Table 5. Antiviral Activity of Vinyl Pyrrolidone Copolymers with Crotonic Acid (VP + KK) or Crotonaldehyde (VP + KA) As a Function of Age of Mice

| Series of experiments | Weight of mice | Preparation used | Dosage (mg/kg) | Virus | Virus titre (log $LD_{50}$) | Protective effect (log IR) |
|---|---|---|---|---|---|---|
| I | 13—14 | No.28 VP+KK | 350 | Semliki forest | 6,9 | 3,0 |
| | | Control | — | Semliki forest | 9,9 | — |
| | 7—8 | No.28 VP+KK | 625 | Semliki forest | 9,5 | 0,8 |
| | | Control | — | Semliki forest | 10,3 | — |
| II | 13—14 | No.74 VP+KK | 350 | Tick-borne incephalitis | 8,0 | 1,5 |
| | | | — | Absettarov strain | 9,5 | — |
| | 7—8 | No.74 VP+KK | 625 | Absettarov strain | 9,75 | 0,25 |
| | | Control | — | Absettarov strain | 10,0 | — |

The data in Table 6 indicate also high antiviral protection in animals treated with VP copolymer with vinylamine. This table shows that the optimal dose of VP copolymer with crotonic acid is comparatively low (70-350 mg/kg), and that increasing this dose to 1750 mg/kg actually causes a decrease in the protective effect.

Table 6. Delaying Effect of Vinyl Pyrrolidone Copolymers on Development of Infection in Mice Resulting from Semliki Forest Virus

| Preparate No. | Second monomer in copolymer | Copolyme dose (mg/kg) | Logarithm of resistance index considering results on days after infection | | | |
|---|---|---|---|---|---|---|
| | | | 5 | 7 | 10 | 15 |
| II—П/1282 | Vinylamine | 25 | 5,0 | 4,6 | 3,8 | 3,4 |
| 28 | Crotonic acid | 70 | 5,0 | 3,6 | 2,6 | 1,7 |
| 28 | Crotonic acid | 350 | 4,9 | 4,4 | 2,2 | 2,0 |
| 28 | Crotonic acid | 1 750 | 3,3 | 1,8 | 1,9 | 1,9 |

Thus, many of the VP copolymers tested with acids, aldehydes and bases produced a definite degree of resistance to the pathogenic effect of two different arboviruses in mice. Experiments performed specially for this purpose showed that the copolymers in the concentrations used are not capable of inactivating the viruses by direct contact with them in vitro at 37° for 90 min.

The antiviral effect resulting from the copolymers depended on the age of the experimental animals. The protective effect was observed only with preliminary introduction of copolymers and decrease as the time from the beginning of appearance of infection increased. These regularities are characteristic for the antiviral resistance resulting from interferon, as well as from interferon production stimulators -- interferonogens [8]. In connection with this, in the interferonogenic properties of all the polymers listed in Table 1 were tested in chick embryos and chick or mouse embryo cell cultures. However, none of these preparations induced the production of interferon in these systems.

Two copolymers of vinyl pyrrolidone (with crotonic acid or with maleic anhydride) were tested in experiments on mice weighing 16-20 g. After intraperitoneal injection of these copolymers in doses of 100 mg/kg, within a few hours inhibitor activity was discovered in the blood serum of these animals in respect to mouse encephalomyocarditis virus and vesicular stomatitis virus.

As we can see from Table 7, before introduction of the preparations and 2 hr after their introduction, the serum activity titres were 8-16 $PID_{50}$/ml. After 6- hr, the serum activity reached 24-28 $PID_{50}$/ml, and after 24 hr -- 128-252 $PID_{50}$/ml. In addition to the capability of suppressing platelet formation in various viruses, other properties of

of the inhibitor also indicate its similarity to interferon. The inhibitor was active after dialysis in a cellophane bag for 48 hr against medium No. 199. The activity of the interferon induced by the copolymers was disrupted by more than 50% as a result of holding at pH 2.0 for 24 hr.

The activity of the inhibitor was not related to direct action on the virus, since it appeared after careful washing of the cells after their treatment with dilute serum for 3 hr before introduction of the virus. The effect of trypsin on the inhibitor (1 g/ml, 37°, 1 hr) and heating of the serum at 54° for 1 hr inactivated their antiviral properties. Actinomycin B introduced to the cell culture in a dosage of 0.5 µg/ml 4 hr before introduction of the inhibitor suppressed its activity. These serums were not active in a heterologic chick embryo cell culture against the Chikungunya virus. These properties of the inhibitor, appearing in the mouse serum, show that it is interferon. All of this allows us to assume that the antiviral effect of certain copolymers in the experiments on mice could be a result of their interferonogenic activity.

## Discussion

Merigan [14] and Merigan and Regelson [15] recently reported on the capability of synthetic polymer materials of another class (copolymers of maleic anhydride and bivinyl ether and certain others) to cause the formation of interferon in mouse blood and human blood. The data of these American authors and the results of our work open new possibilities for the production of interferonogens by chemical synthesis.

There are data available on the antiviral properties of certain of the copolymers of vinyl pyrrolidone with crotonic acid which we studied [1, 2]. In the opinion of the authors, these properties are related to the antitoxic effect of the preparations or with their capability to block the sensitive receptors of the cells and, consequently, attachment to them and penetration of the virus into them.

The experimental material presented above indicates the possible significance of a mechanism of antiviral effect of the copolymers of vinyl pyrrolidone with crotonic acid and maleic anhydride which is different in principle, namely their interferonogenic activity. This is indicated not only by the appearance in the blood of interferon in response to the introduction of these materials, but also by the dependence of the effectiveness of their application on the age of the animals, time of introduction and consideration of results on the magnitude of the infecting dose.

Table 7. Interferon Titers (in PI $10_{50}$/ml in Blood of Mice After Injection of Vinyl Pyrrolidone Copolymers.

| Preparation No. | Second Component | Time after Injection of Copolymers (hrs) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 2 | 4 | 6 | 8 | 24 |
| 2 | Maleic Anhydride | <8 | <16 | 16 | 32; 24 | 42 | 128; 165 |
| 20 | Crotonic Acid | <8 | <16 | <16 | 48 | | 252; 188 |

## Conclusions

1. Polyvinyl pyrrolidone and certain copolymers of vinyl pyrrolidone with crotonic acid, crotonaldehyde, maleic anhydride and vinylamine had antiviral activity in experiments on mice infected with tick-borne encephalitis virus and Semliki forest virus under conditions of introduction of the preparation before infection.

2. The antiviral effect of these polymers and copolymers caused a reduction in the lethality of the infected animals and a decrease in the level of accumulation of virus in the blood and brain in comparison with the lethality and level of accumulation of virus for animals which did not receive the preparation.

3. The antiviral effect of these chemical preparations was found to be most clearly expressed in animals of younger age during the first days after one-time injection of the copolymer and when infected with relatively small viral doses.

4. The capability of certain copolymers of vinyl pyrrolidone with crotonic acid (molecular weight 60,000) and maleic anhydride (molecular weight 500,000) to induce the circulation of interferon in the blood of mice was established. The results of experiments with chick embryos and chick and mouse embryo cell cultures were negative.

5. The results of the work present new proof of the possibility of producing interferonogens by chemical synthesis.

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13. ABSTRACT

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| Interferonogens | | | | | | |
| Copolymers | | | | | | |
| Polymers | | | | | | |
| Vinyl pyrrolidone copolymers | | | | | | |