THE ANTIPYRETIC EFFECT OF PYRAMIDON IN VACCINAL FEVER, DINITROPHENOL HYPERTHERMIA AND EXPERIMENTAL DIPHTHERIA INTOXICATION

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The present theory of the reasons for the temperature rise in fever is based on the notion of reactive change in the functional condition of the thermoregulator centers. According to this theory, not every rise of temperature (not associated with external overheating) can be regarded as fever.

For example, the physiological nature of a temperature rise resulting from an increase in thermogenesis so extreme that its compensation exceeds the adaptive powers of thermoregulation has nothing in common with that of the fever reaction. The hyperthermia induced by the administration of 2,4-dinitrophenol (DNP) is a typical experimental example of such a "metabolic" temperature rise.

The main difference in the condition of the thermoregulator apparatus in dinitrophenol hyperthermia and in fever lies in the fact that although the mechanisms of heat emission are strained to the maximum in the former, the increase in thermogenesis is still greater. When the heat emission of the organism is increased by external cooling, hypothermia does not develop [1, 2]. Hyperthermia, however, increases very rapidly when the temperature of the external environment is moderately high [5, 6].

The temperature conditions of the external environment have little influence on the temperature rise in fever.

In order to further characterize the physiological mechanisms of these two conditions, we decided to compare the antipyretic effects of Pyramidon in fever and in DNP-induced hyperthermia.

Reports that the thermoregulator apparatus is disturbed in diphtheria intoxication [5, 6] led us to investigate in addition Pyramidon's effect on the fever attending this intoxication, a question of particular value in analyzing the condition of thermoregulation.

EXPERIMENTAL RESULTS

The experiments were performed on rabbits weighing 2500-2800 g each. The antipyretic effect of Pyramidon on hyperthermia induced by DNP was studied in the first series of experiments, performed on 14 rabbits.

The experiments were conducted as follows: after the administration of DNP (in doses of 15-30 mg/kg) to a rabbit, the changes in its rectal temperature were observed for 6 hr. A few days later, the same rabbit was given a subcutaneous injection of 0.1 g/kg Pyramidon in the form of a 2% solution.

Ten days or more after these control experiments, we performed experiments in which Pyramidon was administered on a background of hyperthermia.

In the control experiments, 30 mg/kg DNP caused a temperature rise of 0.4-0.8° within 30 min. The maximal temperature rise was observed after 2-3 hr (1.9-3.3°), after which the temperature began to decrease. Six hours after the administration of the drug, the temperature became stabilized at a level 0.4-1° higher than the original (Fig. 1a).*

The administration of Pyramidon to healthy animals caused a temperature drop of 1.3-1.8°, the maximal drop being observed after 1-1½ hr; the temperature than began to rise and usually reached the original level in 4-5 hr (Fig. 1b).

When Pyramidon was administered 45 min after the DNP injection (i.e., when the temperature had risen 0.6-0.8°), it did not either reduce the temperature or inhibit its rise. In these cases, the ultimate temperature rise equalled or even exceeded that observed with the administration of DNP alone (Fig. 1c).

The temperature rise caused by the administration of 20 mg/kg DNP (0.5-1.4°) and the time required for the temperature to return to its original level were much less than with the 30 mg/kg dose. However, no reduction of temperature was effected by the administration of Pyramidon after this dose of dinitrophenol either.

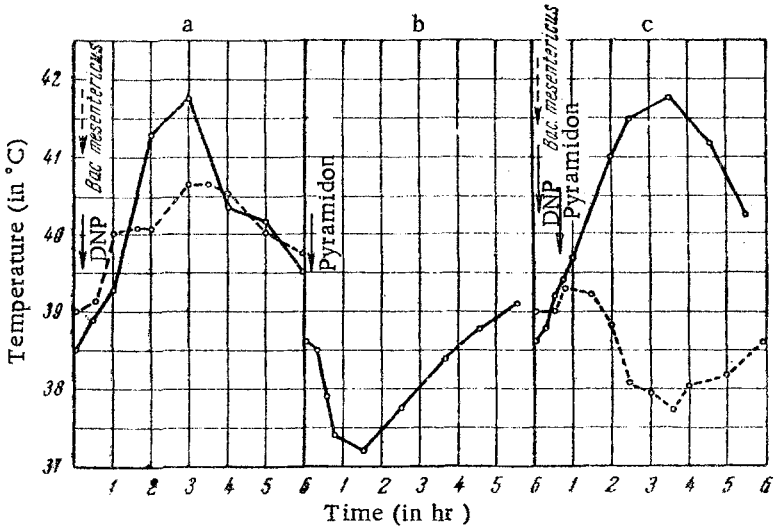

Fig. 1. Effect of Pyramidon on the temperature of normal rabbits given large doses of DNP and in vaccinal fever. a) Temperature curves after administration of 0.03 g/kg DNP (solid line) and 1 ml/kg Bac. mesentericus vaccine (dotted line). Solid arrow – DNP administration; dotted arrow – vaccine administration; b) temperature curve of control animal after administration of 0.1 g/kg Pyramidon (control); c) temperature curves resulting from administration of 0.1 g/kg Pyramidon (thin solid arrow) to rabbits 45 min after injection of 0.03 g/kg DNP (thick solid arrow and solid curve) and one hour after injection of Bac. mesentericus vaccine (dotted arrow and curve).

The 15 mg/kg dose of DNP caused only a slight rise of temperature (0.3-0.7°), the maximum being observed within 2-3 hr (Fig. 2a). As in the preceding experiments, Pyramidon was administered 45 min after the DNP injection, when the temperature rise constituted 0.1-0.3°. The temperature was down to its original level one hour after the Pyramidon injection; the maximal fall (0.5-1.3°), observed 2 hr after the injection, was less than in the control experiments (Fig. 2b). The temperature returned to its original level about 5 hr after the injection (Fig. 2c).

* This and the other figures show individual curves typical for each series of experiments.

A second series of experiments was conducted on eight rabbits in order to determine Pyramidon's antipyretic effect on fever induced by the injection of 1 ml/kg of a Bac. mesentericus culture into the vein of the ear. Our previous investigations have described Pyramidon's effect on this type of experimental fever in rabbits in greater detail.

The culture injection induced a rise of temperature in 30 min. The maximal temperature rise (1-1.5°) was observed after 1½-2 hrs, the original temperature being restored about 6-7 hr after the injection.

A 0.1 g/kg dose of Pyramidon in a 2% solution was administered either 30 min before administration of the pyrogenic vaccine or at the height of the fever. When injected 30 min before the Bac. mesentericus injection, Pyramidon not only prevented the development of the fever reaction, but actually reduced the temperature to 1.1-2.5° below the original level.

When Pyramidon was administered after the injection of the pyrogenic culture, the temperature usually fell 1.5-2° below the original level (see Fig. 1c).

A third series of experiments was conducted on 31 rabbits to study the antipyretic effect of Pyramidon in diphtheria intoxication. The toxin was used in a dilution of 1:100 and injected in a dose of a 3 MLD per animal. The disease was pronounced in the rabbits on the 1st and 2nd days following the administration of the diphtheria toxin, which was clinically apparent from the loss of weight, appetite and muscular tonus and the acute rise of temperature.

Pyramidon was injected daily, either starting the day the toxin was administered or starting the third day of the disease.

When Pyramidon was administered one hour after the toxin was injected, the rabbit's temperature fell to about the same level as in the control experiments (Fig. 3a), returning to the original level in 5-6 hr. When Pyramidon was administered the following day to the same rabbit, the temperature was reduced even more and was still low after 5-6 hr (Fig. 3b). When Pyramidon was again administered on the third day of the disease, when the rabbit's temperature was still low (36.4°), the temperature dropped sharply and showed no tendency to rise even after 6 hr.

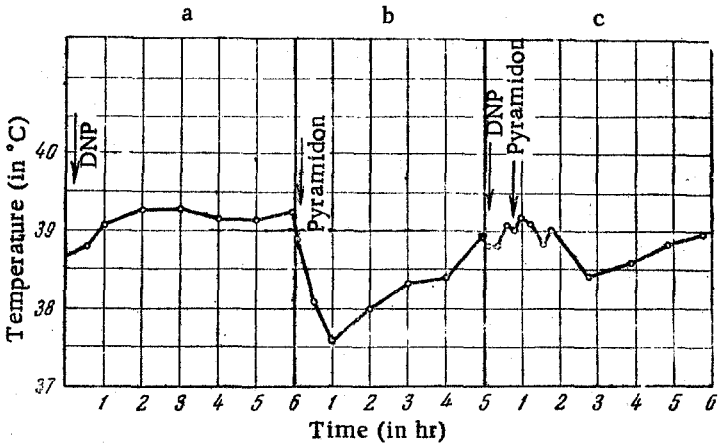

Fig. 2. Change in temperature following administration of Pyramidon to rabbits which had received a small dose of DNP. a) Injection of 0.015 g/kg DNP; b) administration of 0.1 g/kg Pyramidon to control rabbit; c) 0.1 g/kg Pyramidon injected 45 min after injection of 0.015 g/kg DNP.

When Pyramidon was injected for the first time on the third day of the disease, the temperature dropped and remained low until the death of the animal.

The experiments conducted demonstrated that Pyramidon has no effect on dinitrophenol hyperthermia, although it has a sharply pronounced antipyretic effect on both vaccinal and toxic fever. Only with the

administration of a small dose of DNP, 15 mg/kg, the threshold dose required for the development of hyperthermia, was a slight effect observed. The failure of Pyramidon to exert its antipyretic effect with the administration of large doses of DNP is evidently because the thermoregulator apparatus, which was functioning at full capacity even before the administration of the antipyretic, was unable to further increase heat emission.

The data obtained, therefore, show that the temperature rise which follows DNP administration is not due to active reorganization of the thermoregulator apparatus, as is true in the case of fever, but rather to the insufficiency of the adaptive faculties of the thermoregulator apparatus which cannot provide adequate heat emission to balance the excessive heat production induced by the administration of DNP. The temperature drop caused by the administration of Pyramidon in an animal with fever is known to be primarily due to "forced" enhancement of the heat emission processes.

Therefore, the temperature drop induced by Pyramidon in animals injected with the Bac. mesentericus culture or diphtheria toxin and its failure to exert an antipyretic effect in animals which have received DNP are further proof that the mechanism of temperature rise and the functional condition of the thermoregulator center are physiologically different in fever and in dinitrophenol hyperthermia.

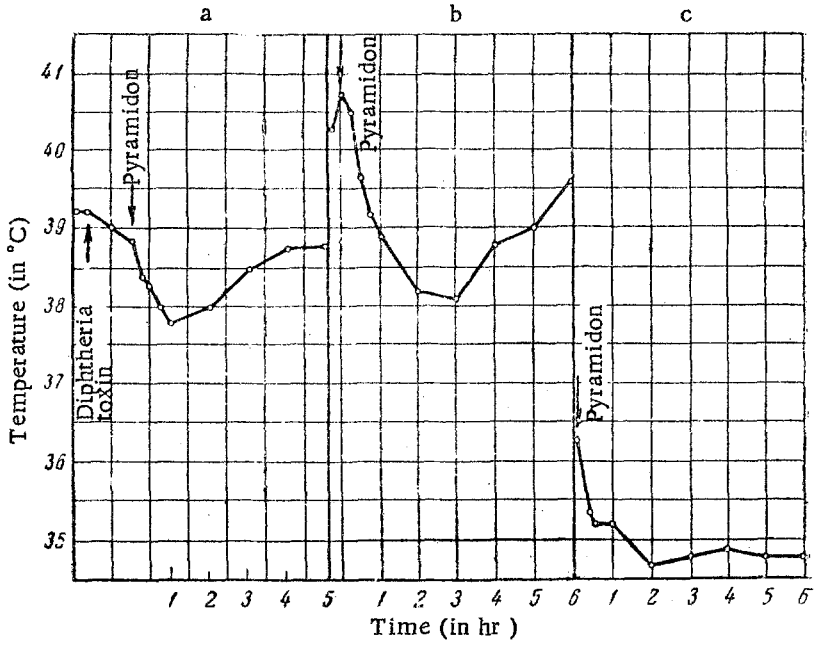

Fig. 3. Temperature change following administration of Pyramidon to rabbits which had received 3 MLD diphtheria toxin. a) 0.1 g/kg Pyramidon administered 2 hr after injection of 3 MLD toxin; b) 0.1 g/kg Pyramidon administered 24 hr after injection of 3 MLD toxin; c) 0.1 g/kg Pyramidon administered 48-72 hr after injection of 3 MLD toxin.

Pyramidon's effect was stronger at the later periods of lethal diphtheria intoxication than at the early and often caused a catastrophic fall of temperature. This further corroborates the literature data [4, 5, 6] to the effect that the functional condition of the thermoregulator apparatus is disturbed in diphtheria intoxication and indicates the great sensitivity of the injured thermoregulator center to the antipyretic.

SUMMARY

Three series of experiments were staged on rabbits. As demonstrated, Pyramidon exerts no effect on development of dinitrophenol hyperthermia; given in the same doses it reduces the temperature of healthy rabbits and especially of those with fever. The sensitivity to Pyramidon rises in toxic injury of the thermoregulation mechanisms (diphtheria intoxication). Experiments confirm the opposite nature of the physiological mechanisms underlying hyperthermia in fever and in toxic rise of thermogenesis under the effect of dinitrophenol.

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