EFFECT OF NITROUS OXIDE ON "SPONTANEOUS" SALIVATION IN DOGS

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Narcotics (alcohol and chloroform) have been shown by S. I. Potekhin [2] and by E. Z. Pushkareva and E. A. Beliavskaia [3] to cause "spontaneous" secretion of saliva in dogs. While studying the effects of nitrous oxide on conditioned reflexes we also observed "spontaneous" salivation, with masticatory movements, in dogs inhaling the gas.

The wide and varied use made of nitrous oxide in medical practice necessitates the detailed study of its effects on the various functions of the organism. The present research is devoted to the study of the nature of "spontaneous" secretion of saliva during inhalation of nitrous oxide, and to the elucidation of its mechanism.

EXPERIMENTAL METHODS

The experiments were performed in a conditioned reflex chamber, on 4 tracheotomized dogs, with a fistula of the parotid gland duct. The animals were prepared for experiment according to the classical Pavlovian procedure, described in N. A. Podkopaev's manual [1]. Mastication, respiration, and secretion of saliva were recorded on a smoked kymograph sheet during the experiments.

Nitrous oxide – oxygen mixtures, containing 20, 40, 60, and 80% of nitrous oxide, were administered without the knowledge of the animals (bypassing the upper respiratory passages), through a special intratracheal cannula, inserted into a tracheotomy incision. The dogs inhaled that mixture from a Douglas bag, or from a gas – oxygen apparatus. This contained meters, permitting of the regulation of the composition and amount of the mixture. Additionally, the composition of the mixture was checked throughout the experiments by means of P. M. Starkov's thermal gas analysis method [6]. In all, we performed 83 experiments with the use of nitrous oxide, and 12 control experiments. In these, the animals inhaled air or oxygen.

EXPERIMENTAL RESULTS

The phenomena of "spontaneous" salivation and mastication were first seen in the dogs Valetka and Mart, using 40% nitrous oxide mixture. In these dogs, we started the flow of gas after the conditioned stimulus had been reinforced by meat-biscuit powder, and after a control test of the conditioned reflex, when the salivation and mastication associated with the act of feeding had entirely ceased. After $\frac{1}{2}$ – 2 minutes of inhalation of 40% nitrous oxide we observed the onset of "spontaneous" salivation and of masticatory movements. The secretion of saliva amounted to 1 – 4 drops per 30 seconds, and the frequency of the masticatory movements to 1 – 5 (observations from 8 experiments). Similar effects were not seen with 20% nitrous oxide mixtures. Taking into account the weakening effect of nitrous oxide on the process of internal inhibition, it might be supposed that the secretion of saliva and the masticatory movements observed during inhalation of 40% nitrous oxide develop as a result of release of inhibition of the temporal conditioned reflex.

In order to check these observations, and for their further study, we repeated the experiments with two other dogs, Laska and Sedoi, which had never been fed under the conditions of the experiment. The experimental procedure was as follows. After preparation, the dogs were left in the stand. We registered the background levels

of salivation and masticatory movements for 5-7 minutes; usually 1 drop of saliva was secreted during 3½ minutes, and there were no masticatory movements. Inhalation of nitrous oxide was then started.

Masticatory movements were seen within 2-3 minutes of inhalation of 40% nitrous oxide. Their frequency varied from 1 to 9 in 30 seconds for Laska (data from 5 experiments) and from 1-12 for Sedoi (data from 6 experiments). "Spontaneous" salivation was not seen for either dog, except for two experiments with Sedoi, in which single drops appeared.

The appearance of "spontaneous" salivation in Valetka and Mart, but its absence in Laska and Sedoi, evidently depended on the different alimentary stimulability of the dogs during the experiment. The alimentary center of Valetka and Mart was highly receptive to stimulation, as a result of the experimental conditions, which always involved the giving of food, with reinforcement of the conditioned stimulus by presentation of meat – biscuit powder 3-5 minutes before administration of nitrous oxide. No such factors were active in the other two dogs, raising their receptivity to alimentary stimuli.

Our further experiments showed that the above interpretation was justified, as after repeated feeding in the harness "spontaneous" salivation was seen in Laska and Sedoi after administration of 40% nitrous oxide, just as for Valetka and Mart. Raising the nitrous oxide concentration of the mixtures to 60 and 80% caused a sharp increase in "spontaneous" salivation and mastication.

At the same time, administration of 60 and 80% nitrous oxide mixtures led to rapid habituation of the animals, shown by the falling off of the secretory and masticatory effects when the experiment was repeated using the same concentration of gas (Fig. 1).

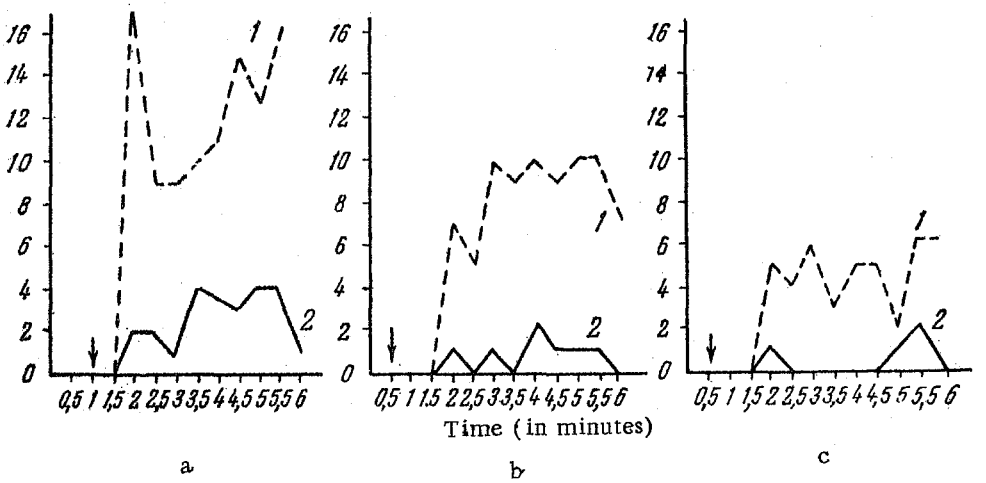

Fig. 1. Recordings of "spontaneous" salivation and masticatory movements in the dog Sedoi during administration of 80% nitrous oxide mixture. a) Experiment No. 23, of February 20, 1954; b) Experiment No. 24, of February 22, 1954; c) Experiment No. 25, of February 23, 1954. 1) Frequency of masticatory movements, 2) amount of "spontaneous" secretion of saliva; the arrows indicate the moment when nitrous oxide was given; the abscissae are time in minutes, and the ordinates express drops of saliva and frequency of masticatory movements.

Our observations show that nitrous oxide, at concentrations of 40, 60, and 80% causes "spontaneous" secretion of saliva and masticatory movements. The intensity of these effects depended on the concentration of nitrous oxide, on the receptivity of the animal to alimentary stimuli, and also apparently on the individual type of higher nervous activity of the given animal.

What is the mechanism of development of "spontaneous" salivation and of masticatory activity during administration of nitrous oxide? V. K. Fedorov [7] ascribed the increase in unconditioned secretion of saliva during

the action of chloral hydrate to the heightened excitability of subcortical centers, following their release from inhibitory control by the cortex. Such an interpretation is supported by the observations of A. I. Smirnov [5] and of T. P. Rolich [4], who found that "spontaneous" salivation appeared in 40-50% of dogs after removal of the cerebral cortex. According to these authors, decerebration raises the sensitivity of the center controlling secretion of saliva to chemical stimuli present in the blood stream.

"Spontaneous" salivation and masticatory movements made their appearance at nitrous oxide concentrations (40, 60, and 80%) at which cortical processes were considerably depressed. It might, in this connection, be supposed that the secretion of saliva and the masticatory movements were due to the enhanced activity of the subcortical alimentary center.

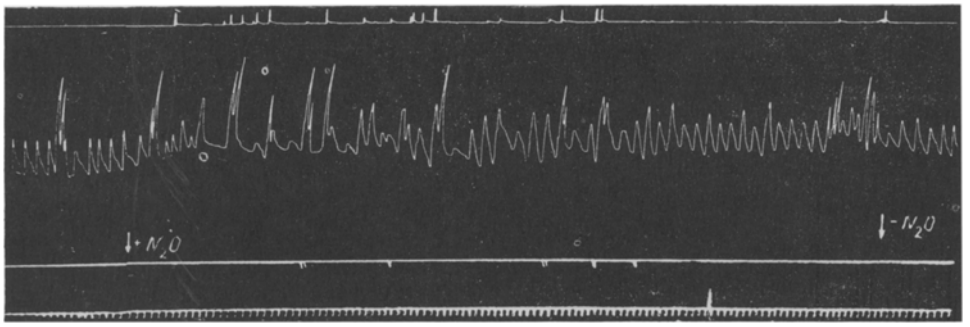

Fig. 2. Salivation and masticatory movements observed when nitrous oxide was passed through the upper respiratory passages of the dog Sedoi (Experiment No. 27, March 8, 1954). Explanation of tracings (from above down): recordings of masticatory movements, recording of respiration, recordings of drops of saliva, time marker (3 seconds).

S. I. Potekhin [2] regarded "spontaneous" salivation of animals given alcohol as being a reflex from the nasal mucosa to stimulation by alcohol.

Nitrous oxide is known to diffuse rapidly and readily through animal tissues. P. M. Starkov [6] showed that it is eliminated through the skin, exposed muscles, and other tissues.

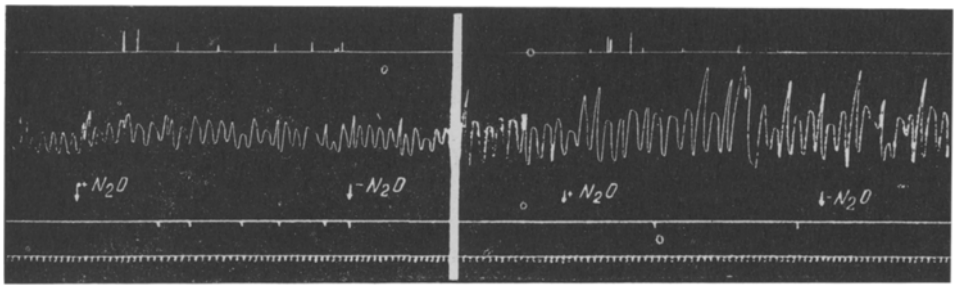

Fig. 3. Salivation and masticatory movements observed during passage of nitrous oxide through the upper respiratory passages of the dog Laska, in Experiments Nos. 52 and 53 on January 28 and 31, 1955. The fall in the magnitude of the effects with repetition of the test is evident. Explanation of tracings as in Fig. 2.

We therefore thought it possible that nitrous oxide might be eliminated from the body through the mucous membranes of the upper respiratory passages, where it might directly stimulate receptors, thus causing reflex "spontaneous" secretion of saliva and masticatory movements.

The following experiments were designed to test this supposition. We inserted two intratracheal tubes into dogs, one being directed toward the lungs, and the other towards the larynx. The dogs breathed in air from the first tube, while pure nitrous oxide was passed into the other, at a rate of 85-250 cc per minute. These experiments were performed on Sedoi, which had had 12 previous exposures to nitrous oxide.

"Spontaneous" salivation and masticatory movements were observed while nitrous oxide was being passed over the mucosa of the upper respiratory passages. The results are shown in Fig. 2.

Repetition of this experiment showed that the magnitude of the response to flow of nitrous oxide through the upper respiratory passages fell from experiment to experiment, salivation no longer appearing during the third test, and mastication during the fifth test.

It seems from our results that the "spontaneous" salivation and the masticatory movements observed in response to stimulation of the upper respiratory passages with nitrous oxide resembled the secretory reflex observed by S. I. Potekhin in response to alcohol, which he considered to be a natural conditioned reflex. In order to elucidate the nature of the reflex we repeated the experiments with the dogs Laska and Topsi, which had not before been exposed to nitrous oxide. These dogs gave no salivary or masticatory response to flow of gas or air through the upper respiratory passages. This result shows that the reflex is not an unconditioned one. Laska was then exposed 12 times to the action of nitrous oxide (60 and 80%). When gas was then passed through the upper respiratory passages salivation and masticatory movements appeared (Fig. 3). As can be seen from Fig. 3 a smaller response resulted from a second passage of nitrous oxide through the upper respiratory passages. No response was seen when the test was repeated a third time.

Our experimental results show that the secretion of saliva and the masticatory movements seen when the upper respiratory passages are exposed to the action of nitrous oxide constitute a natural conditioned reflex, which is elaborated by repeated exposure of the animal to the gas, and which subsequently undergoes extinction.

SUMMARY

Inhalation of nitrous oxide – oxygen mixtures containing not less than 40% of nitrous oxide causes "spontaneous" salivation and masticatory movements in dogs. The magnitude of the response varies with the concentration of nitrous oxide, with the sensitivity to stimulation of the alimentary center, and with the previous conditioning of the animals. The effect is due mainly to strengthening of the function of the subcortical alimentary center, resulting from removal of cortical inhibition. After numerous exposures of the animals to inhalation of nitrous oxide the effects may be elicited by passing the gas through the upper respiratory passages only. This effect is mediated by natural conditioned reflex, which is elaborated by repeated exposure to the gas, and which suffers extinction with further repetition.

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