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MASTER

STUDIES ON THE MECHANISM OF THE EFFECT OF IONIZING RADIATIONS ON THE OLFACTORY SYSTEM

FINAL REPORT

for work accomplished from
January 1, 1967 through
December 31, 1970 on AEC
Contract No. AT(11-1)-1669.

Gary P. Cooper, Ph.D., Principal Investigator
Department of Environmental Health
College of Medicine
University of Cincinnati
Eden and Bethesda Avenues
Cincinnati, Ohio 45219

May 24, 1971

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DISCLAIMER

SCIENTIFIC BACKGROUND

The first observations pertinent to this work were made in 1962 when it was demonstrated that sleeping rats could be aroused by brief exposures to x-rays. Participation of the visual system in the response was precluded since blinded rats responded equally as well as normal ones (12). In another type of behavioral study, x-rays were found to be more readily detected by rats when a small-diameter x-ray beam was oriented to pass through the anterior part of the brain and olfactory bulb than when it was oriented to pass through other parts of the brain and head (6). Subsequently it was shown that ablation of the olfactory bulb virtually abolished the electroencephalographic desynchronization normally observed when sleeping rats are exposed to x-rays (2, 11).

Microelectrode recordings of the activity of single neurons in the olfactory bulbs of anesthetized rats, cats, dogs and rabbits showed that some of the neurons (15-25 percent) responded, usually with an increase in firing rate, when the animals were exposed to x-rays (3,4). In work carried out on the rat, such responses were abolished temporarily by the perfusion of normal saline through the nasal passages of tracheotomized animals, and permanently by the perfusion of ethyl alcohol (3). Responses of many neurons were depressed or abolished by the nasal perfusion of inert gases such as argon and nitrogen (5). These observations indicated that the influence of x-rays is probably exerted on olfactory receptors, and that the effect is a secondary one which is mediated by some radiation-produced chemical agent.

The experiments undertaken in this AEC contract were designed to achieve three main objectives: (1) to more clearly define the site of action of ionizing radiation on the olfactory system, (2) to provide quantitative data relating the radiation dose and dose rate to the olfactory response, and (3) to determine approximately the nature of the radiation-produced olfactory stimulus.

SUMMARY OF RESEARCH ACCOMPLISHED

The following paragraphs briefly present the major results and conclusions of all experiments which were undertaken. Reprints of all published material are

appended to this report to provide more detailed information.

A. Response of Single Olfactory Bulb Neurons in the Rabbit to X- and Beta-Irradiation.

In experiments with anesthetized rabbits the olfactory epithelium was exposed and the response of single olfactory bulb neurons to both 250 KVP x-irradiation and strontium-yttrium beta-irradiation was studied. The results showed that beta-irradiation of the olfactory epithelium evokes responses of olfactory bulb neurons whereas beta-irradiation of the olfactory bulb itself does not. Furthermore, the population of cells which responds to beta rays appears to be identical to that responsive to x-rays. The results of this study provided clear evidence that ionizing radiation stimulates the olfactory system through some action on the olfactory receptors.

B. Quantitative Relationships Between X-Ray Parameters and the Response of Olfactory Bulb Neurons.

In these experiments the response of single olfactory bulb neurons to x-irradiation and beta irradiation was studied in anesthetized rats. The response of single olfactory bulb neurons was studied in relation to the intensity and duration of 250 KVP x-irradiation. It was shown that (a) the frequency of firing of an olfactory bulb neuron is a linear function of the logarithm of the dose rate, (b) there is an inverse relation between the intensity and the duration of x-irradiation required to bring a particular olfactory bulb neuron to a threshold state, (c) the threshold dose for the most responsive units is about 5 milliroentgens, (d) the threshold dose rate for the most responsive units is about 10 milliroentgens per second, (e) the minimum response latency is approximately 125 milliseconds.

These data indicate that the response of olfactory bulb neurons to x-rays may be described by functions similar to those characteristic of other sensory responses. They also provide further indirect support for the contention that responses of the olfactory system to x-irradiation is a consequence of an effect of the x-rays on the olfactory epithelium.

C. X-Rays do not Evoke Responses in Nasal Branches of the Trigeminal Nerve.

The ethmoidal and nasopalatine branches of the trigeminal nerve innervate the nasal mucosa and have been shown to respond sensitively to odors (14). In this experiment we studied the responses of single ethmoidal nerve units to odors, mechanical stimulation, and x-rays. Anesthetized Wistar rats were used. One eye was removed and the ethmoidal nerve dissected free and cut posteriorly. With the head rotated to one side, the orbit served as a convenient recording chamber. Differential recordings were made under oil from fine strands of the ethmoidal nerve.

Those ethmoidal nerve units which innervated the skin responded only to pressure or vibratory stimulation of the skin. Those units which innervated the nasal mucosa responded to a variety of odors tested. Responses to different odors clearly depended on the type of odor and the concentration, with very little difference between units with respect to relative response to a particular odor. No responses to x-ray (250 KVP, 3R/sec) were observed. Therefore, we may conclude that the trigeminal sensory endings either are not sensitive enough to respond to ionizing radiation at the dose rate used (which is far above the threshold for the olfactory system) or that the quality of the radiation stimulus simply is not appropriate for the trigeminal system.

D. Immediate Respiratory Changes Resulting from Olfactory Stimulation by X-Rays.

In previous experiments we noticed that changes in respiratory rhythm sometimes occurred immediately upon exposure of anesthetized rats to x-rays. The experiment described here was designed to investigate this phenomenon in its own right. Lightly anesthetized and unanesthetized rats were given 3-second x-ray exposures (250 KVP,3 R/sec.) and their respiratory movements recorded with an impedance pneumograph.

An increase in respiratory rate occurred in both lightly anesthetized or unanesthetized rats within 0.5 seconds after the beginning of x-irradiation of the whole animal. Irradiation of the body only was ineffective. Experiments with rats having lesions of the olfactory bulbs or lesions of the cerebral cortex revealed that the respiratory changes were largely, if not entirely, due to olfactory stimulation by x-rays. Thus, the arousal effect of olfactory stimulation by ionizing radiation is sufficiently strong to evoke immediate and striking alterations in respiratory rate even in anesthetized animals.

E. Effects of High-Dose X-Irradiation on Olfaction in Rabbits.

While it is now known that the olfactory system is very responsive to low doses of ionizing radiation, there have been no previous experimental studies devoted to the effects of high doses of radiation on the olfactory response to odors. Therefore, responses of the olfactory system to strong odor stimulation were studied in anesthetized rabbits immediately after x-irradiation (250 KVP) of the head. Since the olfactory system is so sensitive to ionizing radiation it might have been supposed that harmful effects on the system would be observed at relatively low doses. But, this study showed that such is not at all the case. Acute abolition of olfactory bulb response to strong odor stimulation in rabbits did not occur until head-only exposure doses in excess of 50 KR had been given over an exposure period of 2 to 4 hours. Slightly higher doses were required to abolish immediately all neuronal response to odor, as determined by microelectrode recordings of single olfactory bulb neurons. Response failure was due primarily, if not entirely, to effects of radiation on the olfactory bulb, since olfactory receptor responses to odor were readily obtained following x-ray doses as great as 95 KR and after abolition of all responses in the olfactory bulb.

These data show that the peripheral olfactory system, like most other peripheral nerves and receptors, appears to be considerably more radioresistant than the central nervous system. The x-ray required to abolish olfactory bulb response to odor were equal to or greater than those observed in previous work to produce acute neurological signs, central nervous system damage, and death when the heads of rabbits and other animals were exposed to x- and gamma radiation (8,9,10).

Since the data show that the dose required to abolish odor response is approximately 10^7 to 10^8 times the dose required for a threshold response of the system to x-rays (1,13), we concluded that the extreme sensitivity of the olfactory system to x-rays was not a consequence of its being easily damaged by radiation.

F. Response of Olfactory Bulb Neurons to X-Rays as a Function of Nasal Oxygen Concentration.

Much of the data discussed above implicate an effect of ionizing radiation on olfactory receptors. But the question remained of precisely what the radiation-produced stimulus actually is and where it is produced. In the experiment described in this section an initial attack on

these problems was made. The purpose of the experiment was to determine whether the concentration of oxygen in gas flowing through the nasal cavities influences the strength of response of olfactory bulb neurons to x-rays.

Recordings were made from single olfactory bulb neurons in anesthetized rats. The trachea of each rat was severed and both ends were cannulated. The animal breathed room air through the caudal cannula. The rostral cannula was connected to a gas perfusion system which permitted the nasal perfusion of either odorized or unodorized gas containing any concentration of oxygen. The x-ray dose rate was 90 roentgen/min (250 KVP).

The results of the experiment are significant in that they clearly show that the response to radiation is unaffected until the oxygen concentration is decreased to about 2 percent, below which the response decreases dramatically until at 0 percent oxygen it is only 30 percent as large as responses obtained with 10 percent oxygen. The response functions closely resemble the "oxygen effect" curves obtained in a variety of other radiobiological experiments. We concluded that ionizing radiation probably stimulates olfactory receptors by the production of some chemical substance through reactions which require, or are facilitated by, oxygen.

G. Similarity of X-Ray and Ozone as Olfactory Stimuli.

The outcome of the study described in the preceding section, which establishes the importance of oxygen in the olfactory response to radiation and the finding of Gasteiger and Helling (7) that ambient ozone selectively masks x-ray detection in rats, led to the design of another experiment intended to further clarify the nature of the radiation-produced olfactory stimulus. In this experiment the qualitative nature of the x-ray stimulus was investigated by comparing the responses of olfactory bulb neurons to x-ray, ozone, and amyl acetate. Responses of olfactory bulb neurons were studied in 20 adult, anesthetized, Wistar rats. Three standardized olfactory stimuli were used: (a) 250 KVP x-irradiation of the head at a dose rate of 1.5 R/sec, (b) 2 parts per million ozone, and (c) amyl acetate in a concentration of 10^{-2} of vapor saturation at 25°C. The results show that those units which respond best to x-ray also respond most sensitively to ozone. On the other hand those neurons which respond best to amyl acetate usually respond poorly to both ozone and x-ray.

These results again support the indirect-action hypothesis and indicate that ozone or some similar radiation chemical product may be responsible for olfactory stimulation by ionizing radiation.

REFERENCES

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