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Effects of 4-Dimethylaminophenol on Blood Flow and Blood Gases in the Brain

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Summary. The effects of i.v. injected 4-dimethylaminophenol · HCl, a ferrihemoglobin-forming substance, on cerebral blood flow, brain temperature, blood gases, and lactate concentration in the sinus sagittalis blood were measured on male beagle dogs anesthetized with chloralose.

An increase in cerebral blood flow became measurable when 5% or more of the hemoglobin was oxidized to ferrihemoglobin. The local cerebral blood flow of the cingulum region and the flow in the sinus sagittalis increased, while the sinus pO_2 decreased. An increase in the ferrihemoglobin content of some 20% of the total hemoglobin at a constant arterial pO_2 and pCO_2 was attended with a decrease in the sinus pO_2 of about 10 mm Hg when less than 40% of the heme iron was oxidized. The sinus pO_2 approached a threshold value of some 8 mm Hg when the ferrihemoglobin content was increased above 40%. The lactate concentration began to rise very rapidly when 40–50% of the hemoglobin was oxidized. At the same time pCO_2 increased and pH decreased in the sinus blood. The brain temperature remained unchanged. The behavior of conscious dogs with a ferrihemoglobin content of 40% of the total hemoglobin showed no abnormalities.

Key words: 4-Dimethylaminophenol – Ferrihemoglobin – Cerebral blood flow – Blood gases

Introduction

4-Dimethylaminophenol · HCl (DMAP) is a substance that produces very rapidly ferrihemoglobin (Kiese and Weger 1969). Its action on various physiologic parameters has been investigated in chloralose-anesthetized dogs (Klimmek et al. 1979a, b). Since ferrihemoglobin formation entails a reduction in the oxygen capacity of the blood it is of interest to know how the oxygen supply to the brain is maintained.

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The influence of ferrihemoglobinemia on the venous pO_2 and blood flow of the brain has been interpreted so far on the basis of the experiments of Noell (1944) who lowered the oxygen capacity of canine blood by bleeding and substituting Ringer solution under normoxic conditions but did not produce ferrihemoglobin.

In contrast to other ferrihemoglobin-forming substances, e.g., nitrites with their well-known severe negative effects on the circulation, the absence of such alterations after i.v. injection of DMAP makes it a useful tool to study the response of the brain to lowered oxygen capacity that is not overshadowed by circulatory depression and/or arterial hypoxia.

The present study should contribute to elucidate the cerebral response to ferrihemoglobinemia due to treatment or poisoning with ferrihemoglobin-producing agents.

The sensitivity of the cerebral cortex to oxygen deficiency led us to choose the cortex region in the canine brain to clarify the consequences of a decrease in oxygen capacity. For the determination of cerebral blood flow we compared the thermoelectric (Gibbs 1933/34) and the electromagnetic method with each other. The sinus sagittalis is for the most part responsible for the drainage of the cortex (Ingvar 1958). To make a comparison of both methods as reliable as possible the thermocouple tips were placed in the cingulum, that belongs to the region drained by the sinus to which the electromagnetic flow probes were attached. In addition, blood gases and lactate concentration were determined in the arterial and sinus blood.

Materials and Methods

Male beagle dogs weighing 12.5 ± 0.3 kg (mean $\pm$ SE) were anesthetized with thiopental-Na (10 mg/kg i.v.) and chloralose (α-D(+)-gluco-chloralose, dissolved in propanediol-1,2, 50 mg/kg i.v.). Administration of the anesthetic was repeated as required. After endotracheal intubation most of the dogs were allowed to breathe spontaneously; part of them was ventilated with room air by a Schuler respirator (Braun-Melsungen) after relaxation with alcuronium · HCl. Half of the initial dose of alcuronium · HCl (0.04 mg/kg i.v.) was administered at 20 min intervals.

Excepting the experiments with thermocouples clotting of the blood was prevented by heparin (500 U.S.P.-U/kg i.v.), whose administration was repeated every hour (250 U.S.P.-U/kg i.v.).

Ferrihemoglobin was determined by the increase in absorbance at 546 nm after addition of KCN to hemolyzed blood. Total hemoglobin was determined as ferrihemoglobin after oxidation of the ferrohemoglobin with potassium hexacyanoferrate (III). Blood lactate was measured with Biochemica-Test-Combinations (Boehringer-Mannheim, FRG) by the reaction with lactate dehydrogenase.

The dogs lay in a hanging device. The muzzle was fastened by a leather band on a molded metal plate, and the head was held by two bars from both sides on the level of the ears.

A hole was drilled in the crista sagittalis to admit the insertion of a tube into the sinus sagittalis. Sinus sagittalis and jugular vein were connected with each other by an anastomosis in which pressure and flow were measured by a pressure transducer (Statham) and an electromagnetic flow probe (Hellige).

pO_2, pCO_2, and pH of the sinus blood were determined continuously with a micro blood-gas analyzer (Gas Check AVL). For this purpose sinus blood was pumped through the measuring chamber of the analyzer and returned to the anastomosis. In addition, blood-gas analysis was also carried out in the carotid artery, immediately before and after the measurements in the sinus blood.

Local cerebral blood flow was determined with thermocouples according to Hensel (1961), who has modified the needle flow recorder presented by Gibbs in 1933.

The thermocouple unit was produced by Hartmann and Braun, Frankfurt/M. The copper and constantan wires together with two heating wires for alternate heating of the thermojunctions were incorporated and insulated in two equidistant stainless cannulas.

The scalp was dissected over the crista sagittalis, and the tissue was removed from the skull on both sides of the sagittal suture. On the right hemisphere, before the protuberantia occipitalis externa and 0.5 cm beside the sagittal suture, two channels of 1 mm in diameter and 1.3 cm in distance were bored vertically in the skull. The tips of the thermocouple cannulas were inserted into the bore holes and pushed forward by 1.5 cm through the gyrus marginalis before being stopped in the cingulum. In a similar manner another thermocouple was inserted into the left hemisphere for measurements of the absolute brain temperature.

Bleeding in the skull was prevented by a powder mixture containing $FeCl_3$, dichlorophen, and thrombin (Thrombo-Tuffon). Besides its action as accelerator of coagulation the powder was sufficient to seal the bore holes and to stabilize the temperature curves that otherwise showed oscillations due to the influence of the room air.

The absolute temperature and the temperature difference between the heated and unheated thermojunctions were recorded by the Fluvograph 2 (Hartmann and Braun, Frankfurt/M). From the temperature difference δ the heat conductivity λ was calculated by the formula

$$\lambda = K_1 \cdot \frac{I^2}{\delta} - K_2.$$

The heat conductivity has the dimension cal $cm^{-1}s^{-1}\,°C^{-1}$, K_1 [cal $cm^{-1}s^{-1}A^{-2}$] is a constant depending on the physical structure of the heated thermojunction and on its distance from the reference thermojunction. I [A] is the intensity of the current and was adjusted to 13 mA, resulting in a temperature difference of 2° C between the thermojunctions. K_2 [cal $cm^{-1}s^{-1}\,°C^{-1}$] compensates for the mistake brought about by the thermic short circuit when the heated thermocouple is put in a medium whose heat conductivity is zero. The resolving power of the potentiometer was 0.02° C.

After the experiment in anesthesia the dogs were killed by i.v. injection of saturated KCl solution. The thermocouples were removed and the remaining channels were injected with a suspension of charcoal to make possible the localization of the thermocouple tips. The charcoal-marked right hemisphere was histologically examined after fixation in formaldehyde solution and embedding in paraffin. A cubic brain piece of about 2 cm in diameter was cut out from the cingulum of the left hemisphere. The brain tissue, stored in 0.9% NaCl solution under room air, was equilibrated at various temperatures in a water bath. The heat conductivity of the dead brain and its temperature were determined in the above-mentioned manner.

λ_{100} is the heat conductivity of the living anesthetized brain before any treatment, λ_0 is the heat conductivity of the dead brain. $\Delta\lambda_{100}$ equals the difference between λ_{100} and λ_0 and is a parameter for the local resting blood flow in the brain. For graphic representation each change $\Delta\lambda$ at any time is related to $\Delta\lambda_{100}$. Thus, the per cent change in the resting heat conductivity $\Delta\lambda_{100}$ is obtained as measure for the change in local cerebral blood flow. The data are presented as arithmetic means ± standard error (SE).

Results

1. Measurements with Thermocouples in the Brain

Table 1 shows the averaged values for heat conductivity in living and dead brains and their difference as measure for local resting cerebral blood flow. In the range 35–39° C the heat conductivity λ_0 was independent of the tissue temperature in vitro. Changes in brain temperature of 0.49 ± 0.17° C, observed over a 60-min period in four anesthetized dogs, were not accompanied by any variation in heat conductivity.

	λ_{100} $\frac{\text{cal} \cdot 10^{-4}}{\text{cm} \cdot \text{s} \cdot °\text{C}}$	λ_0 $\frac{\text{cal} \cdot 10^{-4}}{\text{cm} \cdot \text{s} \cdot °\text{C}}$	$\Delta\lambda_{100}$ $\frac{\text{cal} \cdot 10^{-4}}{\text{cm} \cdot \text{s} \cdot °\text{C}}$
n	33	33	33
Mean	12.85	11.51	1.33
± SE	0.10	0.05	0.09

Table 1. Heat conductivity in the living brain (λ_{100}) of chloralose-anesthetized dogs, heat conductivity in the dead brain (λ_0) of these dogs, and their difference ($\Delta\lambda_{100} = \lambda_{100} - \lambda_0$) as measure of resting cerebral blood flow in the cingulum region

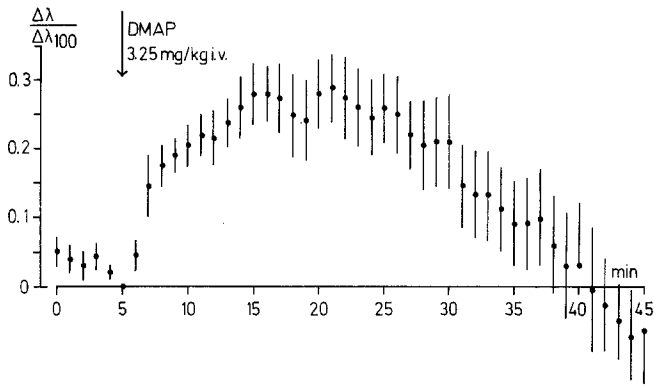

Fig. 1. Changes in local cerebral blood flow, illustrated by relative changes in heat conductivity $\frac{\Delta\lambda}{\Delta\lambda_{100}}$ in the cingulum region of chloralose-anesthetized dogs, before and after DMAP, 3.25 mg/kg i.v. Means ± SE; $n = 5$

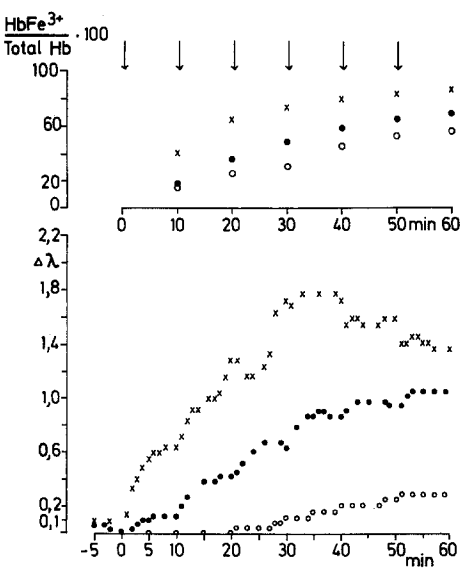

Fig. 2. Ferrihemoglobin content in venous blood and absolute changes in heat conductivity in the cingulum region of three chloralose-anesthetized dogs after repeated injection of DMAP *(arrows)* in 10-min intervals, 1 mg/kg ○, 1.5 mg/kg ●, 3 mg/kg ×

The histological examination of brain tissue gave no signs of edema, hemorrhage, or cellular infiltration. The insertion channels of the thermocouple needles were marked by charcoal pigment and partly contained erythrocytes.

The heat conductivity increased by $29.5 \pm 5.4\%$ above the resting level within 15 min and reverted to the initial level within further 30 min in the dogs that were injected with DMAP (3.25 mg/kg) (Fig. 1). Repeated injections of 1, 1.5, or 3 mg DMAP/kg in 10-min intervals (Fig. 2) induced always an additional increase in heat conductivity ($\Delta\lambda$) as long as the ferrihemoglobin content was clearly below 80% of the total hemoglobin. Injections of DMAP causing higher contents of ferrihemoglobin were followed by a gradual decrease in heat conductivity. From Fig. 2 emerges that there must be a threshold value for the content of ferrihemoglobin above which the heat conductivity begins to rise. To find out the approximate value for this threshold, two dogs were given DMAP in doses of 0.5 and 0.75 mg/kg that lead to maximal ferrihemoglobin contents of 8.4 and 13.2%, respectively, without causing any changes in heat conductivity, respiratory minute volume, or heart rate. Another two dogs were administered 1 mg DMAP/kg that oxidized 16.8 and 18.2% of the total hemoglobin. The heat conductivity increased in both animals, but respiratory minute volume and heart rate remained unchanged. The mean arterial pressure was not influenced in the above mentioned range of the ferrihemoglobin content.

The brain temperature ($35.53 \pm 0.76°$ C) did not vary in the dogs that were given DMAP (3.25 mg/kg).

2. Measurements in the Sinus Sagittalis

In addition to the determination of local cerebral blood flow with thermocouples, blood flow, blood pressure, pO_2, pCO_2, and pH were measured in the sinus sagittalis.

Repeated Injection of DMAP (1.5 mg/kg i.v.) Every 10 min During Artificial Respiration

The coincidence of the elevation of heat conductivity, i.e., local cerebral blood flow and higher ferrihemoglobin content (Fig. 2), was reinvestigated in the sinus sagittalis. By artificial respiration the arterial blood gas values could be kept stable and a compensatory respiratory response to the decrease in the blood oxygen capacity during ferrihemoglobin formation was avoided. Each injection of DMAP (1.5 mg/kg) was followed by an increase in the ferrihemoglobin content of the sinus sagittalis blood up to a maximum of $64.9 \pm 2.1\%$ of the total hemoglobin (Fig. 3) after the fifth dose while the total hemoglobin content itself (13.7 ± 0.5 g/100 ml of blood) did not change. The blood flow in the sinus sagittalis (Fig. 3) increased consistently to maximally 188% above the initial value and was attended with a rise in the sinus blood pressure from 1.4 ± 0.2 to 1.8 ± 0.2 mm Hg.

The regression line for the relationship between sinus blood flow y [ml/min] as dependent variable and ferrihemoglobin content x [g/100 ml] as independent variable was estimated as $y = 0.98x + 5.33$, in other words, the sinus blood flow

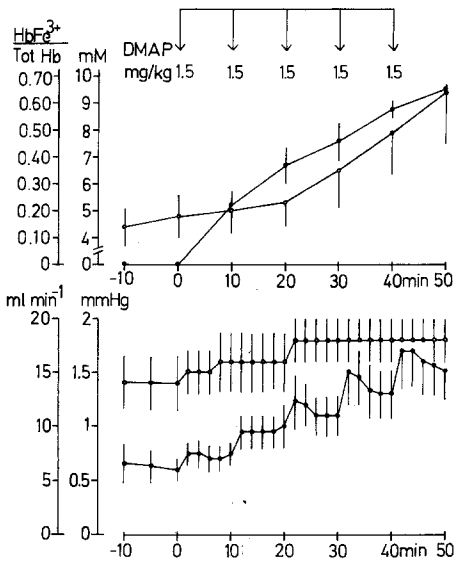

Fig. 3. Ferrihemoglobin content ●—● and lactate concentration ○—○ (upper part), blood pressure ○—○ and blood flow ●—● (lower part) in the sinus sagittalis of artificially ventilated dogs under chloralose anesthesia after repeated injection of DMAP *(arrows)* , 1.5 mg/kg i.v., in 10-min intervals. Means ± SE; $n = 4$

increased by 1 ml/min when the ferrihemoglobin content increased by 1 g/100 ml of blood.

The sinus pO_2 (Fig. 4) decreased from 30.1 ± 1.1 to 18.6 ± 1.5 mm Hg after the first injection of DMAP and from 18.1 ± 1.2 to 11.2 ± 1.3 mm Hg after the second injection. Further injections induced only a slight drop of pO_2 whose lowest value averaged 8.4 ± 0.9 mm Hg. After 50 min pO_2 began to rise. The sinus pCO_2 and pH did not change until the fourth dose of DMAP had been given (Fig. 4). The rise in pCO_2 was accompanied by a decrease in pH and coincided with a high and rapid rise in the sinus lactate concentration to 9.4 ± 1.8 mmol/l (Fig. 3). The arterial lactate concentration, however, increased simultaneously from 2.4 ± 0.4 to 2.8 ± 0.5 mmol/l only.

The increase in pCO_2 could not be reproduced in vitro when 1 mg DMAP/0.1 ml of 0.9% NaCl solution was added to 5.5 ml of canine blood that circulated through the measuring chambers of the blood-gas analyser; hereby 87% of the total hemoglobin was oxidized to ferrihemoglobin. On the contrary, the pCO_2 increased by 21, 20 and 21 mm Hg each when lactic acid (27.8 µmol in 2.3 µl) was added thrice to 5.5 ml of canine blood in vitro.

The values for pO_2, pCO_2, and pH in the carotid artery before and after the blood-gas analysis in the sinus sagittalis blood averaged 71.5 ± 2.4 mm Hg, 47.3 ± 2.8 mm Hg, and 7.28 ± 0.02, respectively.

Infusion of DMAP (0.2 mg kg^{-1} min^{-1} i.v.) During Artificial Respiration

Since local cerebral blood flow and the blood flow in the sinus sagittalis had increased when 20% of the total hemoglobin was oxidized, the infusion of DMAP

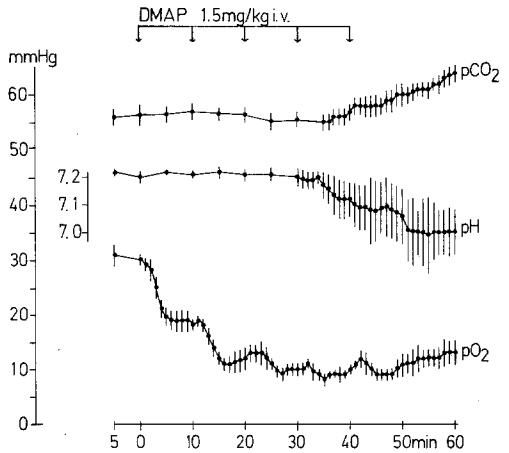

Fig. 4. PO_2, pCO_2, and pH in the sinus sagittalis of artificially ventilated dogs under chloralose anesthesia after repeated injection of DMAP *(arrows)*, 1.5 mg/kg i.v., in 10-min intervals. Means ± SE; $n = 4$

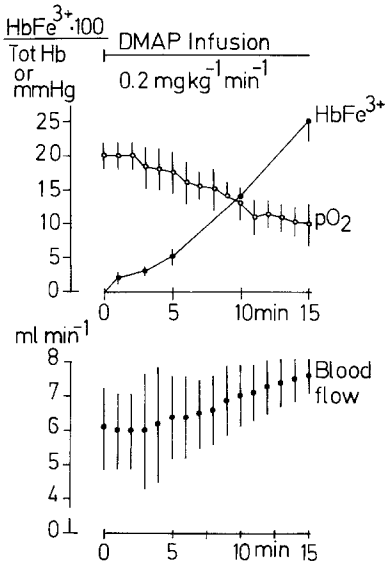

Fig. 5. Ferrihemoglobin content, pO_2, and blood flow in the sinus sagittalis of artificially ventilated dogs under chloralose anesthesia during infusion of DMAP (0.2 mg kg^{-1} min^{-1}). Means ± SE; $n = 3$

served to find out the threshold value for the ferrihemoglobin content that may induce a higher sinus blood flow.

The ferrihemoglobin content increased to 25.2 ± 3.1% at 15 min (Fig. 5). The sinus blood flow began to increase when more than 5% of the total hemoglobin was oxidized (Fig. 5). No change in the sinus blood pressure or the lactate concentration was found while the pO_2 (Fig. 5) decreased from 19.6 ± 1.9 mm Hg to 10.1 ± 2.8 mm Hg; pCO_2 and pH did not change. The values for pO_2, pCO_2, and pH in the carotid artery before and after the blood-gas analysis in the sinus blood were 78.1 ± 4 mm Hg, 33.7 ± 0.7 mm Hg, and 7.38 ± 0.03, respectively.

3. Behavior of Conscious Dogs

Eight conscious dogs injected with a single dose of DMAP, 3.25 mg/kg i.v., that induces the oxidation of 40% of the total hemoglobin, showed no abnormalities in muscular coordination or general behavior. DMAP, 1.5 mg/kg i.v., was administered to four conscious female dogs in intervals of 10 min so that a ferrihemoglobin content of $73.8 \pm 2.7\%$ of the total hemoglobin was reached after 50 min. Restlessness, ataxia, hypersalivation, throng to defecate, urination, and defecation occurred when about 60% of the hemoglobin was oxidized. The plantar tendon reflex and the reaction to pain stimuli was unaffected. All dogs recovered completely.

Discussion

The heat conductivity of the dead brain tissue of 11.5 ± 0.05 cal 10^{-4} cm^{-1} s^{-1} $°C^{-1}$, presented in Table 1, is identical with the data found by Golenhofen et al. (1963) for the canine brain.

The initial values for pO_2 (30 mm Hg) and pCO_2 (55 mm Hg) in the sinus sagittalis are in accordance with the values measured by Noell and Schneider (1943, 1948) in the canine brain and Gibbs et al. (1942) in the blood of the internal jugular vein of human subjects.

DMAP causes a long-lasting, reversible increase in cerebral blood flow. This could be demonstrated by two methods, the determination of heat conductivity and the electromagnetic measurement of sinus blood flow. Both methods proved to be reliable in yielding qualitatively comparable results. It must be borne in mind that the thermoelectric method adapted to the brain is not quantitative because the calibration raises problems that have not been overcome as yet (Betz and Hensel 1962). On the other hand, our experiments with DMAP have confirmed the usefulness of the thermoelectric method for the evaluation of pharmacodynamics. The increase in cerebral blood flow after injection of DMAP is related to the ferrihemoglobin content in the blood and becomes measurable when about 5% or more of the total hemoglobin is present as ferrihemoglobin. Several times, the initial increase in flow was followed by a slight diminution; this may be regarded as a reflex overcompensation followed by a stabilization on a lower level as the ferrihemoglobin formation due to DMAP shows an initial very rapid increase (Kiese and Weger 1969). The pO_2 on the venous side of the capillaries is of great importance in the control of cerebral blood flow (Opitz and Schneider 1950). Lowering of the O_2-capacity by ferrihemoglobin formation results in a more pronounced decrease in venous pO_2 than may be expected from the same decrease in the O_2-saturation of hemoglobin by breathing an O_2-N_2-mixture, since the O_2-dissociation curve of hemoglobin is shifted to the left in the presence of ferrihemoglobin (Darling and Roughton 1942). This must be taken into account for the evaluation of the pattern of pO_2 after each injection of DMAP.

Below a ferrihemoglobin content of 40% the oxidation of about 20% of the heme iron entailed a decrease in the venous pO_2 of about 10 mm Hg. Above a ferrihemoglobin content of 40% the sinus pO_2 did not substantially decrease below

10 mm Hg (Fig. 4) although the augmentation of the ferrihemoglobin content proceeded (Fig. 3). This fact may be explained by a lowered binding of O_2 to hemoglobin due to the diminution of pH produced by lactic acidosis and the rise in pCO_2. 5–10 mm Hg for the sinus pO_2 is apparently a threshold value that is in accordance with the "lethal threshold" of the same order of magnitude assumed by Noell and Schneider (1943) and Opitz and Schneider (1950).

The lactate concentration as an indicator of oxygen debt increased conspicuously in the sinus blood when the ferrihemoglobin content had risen to 40–50% of the total hemoglobin and the pO_2 in the sinus blood had fallen to about 10 mm Hg. As the penetration of lactate through the blood-brain barrier is retarded (Schmahl et al. 1966) lactate may have already been accumulated in the brain tissue at a lower ferrihemoglobin content before appearing in the sinus blood. This also would account for the failure of changes in the sinus pH despite the fall of the sinus pO_2 below the critical threshold of about 20 mm Hg (Noell 1944; Noell and Schneider 1943).

During hypoxia pCO_2 is not increased in the tissue (Betz and Kozak 1967). But it cannot be excluded that the buffer capacity of the extracellular space may be exhausted by acidic metabolites so that transiently more CO_2 may be released that would diffuse into the venous capillaries. If this really happened the freely diffusing CO_2 would be expected to appear before the lactate enters the venous blood. The stability of pCO_2 in our experiments does not allow to establish evidence for it. pCO_2 also was independent of comparable changes in sinus blood flow after several injections of DMAP.

The addition of lactic acid to venous blood in vitro to such an extent that the lactate concentration is comparable to that measured in vivo has shown that the striking increase in pCO_2 in vivo and the concomitant decrease in pH may be accounted for by the consumption of bicarbonate buffer due to decompensated metabolic acidosis. Ferrihemoglobin is obviously not involved in the release of CO_2 since DMAP had no such effect in blood in vitro. Probably, the excess CO_2 contributes to the rise in cerebral blood flow by its vasodilator action on the cerebral vessels, thus constituting a final step in the control of the blood flow increase during hypoxia and anoxia.

According to Thews (1960) a venous pO_2 of 17–19 mm Hg (critical threshold) in the human brain should cause loss of consciousness and a pO_2 of 12 mm Hg (lethal threshold) should entail immediate danger of life. If this were true the diminution of pO_2 to 10 mm Hg in the sinus blood as observed in the anesthetized dogs should be accompanied by evident symptoms from the central nervous system in conscious dogs. The normal behavior of the conscious dogs and the young adult human subjects treated with DMAP, 3.25 mg/kg i.v. (Weger 1969), that induced a ferrihemoglobin content of 30–40% of the total hemoglobin without provoking a decrease in blood pressure, is in contradiction to the prediction made by Thews. Clear-cut symptoms of cerebral anoxia did not appear until 50–60% of the hemoglobin iron was lost for the oxygen transport. It is apparent that the conclusions drawn by the same author from calculations that were based on Krogh's cylinder model and the data given by Opitz and Schneider (1950), who also did their experiments on chloralose-anesthetized dogs, are not suitable to

predict how the brain will be provided with oxygen when ferrihemoglobin has been produced by DMAP.

Similar doubts about the practical significance of the theoretical O_2-diffusion model in vivo have been put forward by MacMillan and Siesjö (1971), who were not able to ascertain a change in the content of ATP, ADP, and AMP and in the relation [NADH]/[NAD^+] in the rat brain even when the arterial pO_2 had been lowered to less than 20 mm Hg.

Obviously, the regulatory mechanisms that are responsible for the control of cerebral oxygen supply are very sensitive to even small changes in the ferrihemoglobin content. Despite a very low pO_2 in the brain cortex of 10–15 mm Hg waking consciousness can be guaranteed in a wide range of ferrihemoglobinemia, up to 30–40% of the total hemoglobin. Above this range the brain begins to incur an oxygen debt.

The results suggest that ferrihemoglobinemia below 40% of the total hemoglobin in acute poisoning with toxic agents is per se no reason to dramatize the oxygen supply to the brain. This probably also holds true for the administration of DMAP as an antidote against poisoning with lethal doses of cyanide, that require a rapid ferrihemoglobin formation for a complete detoxication of cyanide.

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