Effect of Dextran on Cerebral Function and Blood Flow after Cardiac Arrest. An Experimental Study on the Dog

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SUMMARY EEG activity and regional cerebral blood flow were monitored during 5 hour survival following cardiac arrest in 32 pentobarbital anesthetized mongrel dogs. The animals were mechanically ventilated and blood gases were maintained at physiologic levels. Regional cerebral blood flow and cardiac output were measured using 15 µm microspheres. EEG was recorded from 6 epidural electrodes using bipolar techniques.

The animals were divided into 3 groups. The animals in Group I had an arrest of 8–11 minutes and those in Group II and III had an arrest of 12–16 minutes. Group II animals received no treatment. Group III animals were given 1 g/kg of dextran 40 at a concentration of 10% in normal saline following the arrest and maintained with 10 mg/kg/min during the 5 hours of recovery. In Groups I and III there was shorter duration of a flat EEG and 5 hours after the arrest the EEG activity was closer to normal than in Group II. After 5 hours the EEG scores of Group III were significantly greater than Group II (p < 0.03). The cortical grey matter and hippocampus had the greatest reduction of blood flow following cardiac arrest. The mean cortical grey matter blood flow in Group II was less than in Groups I and III at 3 hours. After 5 hours the grey matter blood flow was greater in Group III than in Group II (p < 0.09).

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LOW MOLECULAR WEIGHT dextran 40 (Rheomacrodex) has been shown to diminish mortality and to enhance the quality of survival when given to patients following acute stroke. Experimental study also has shown that administration of this hemodiluting agent following cerebral arterial occlusion reduced the circulatory impairment at the microvasculature level. Dextran’s effectiveness may be related to its action in reducing blood viscosity and increasing plasma volume; to its effect in minimizing aggregation of formed blood elements; or to an antplatelet aggregation effect. These actions suggest that low molecular weight dextran may be of value in the treatment of the brain injury induced by circulatory arrest, particularly if “no reflow” is an important cause of such injury.

Methods

Thirty-two nonheparinized mongrel dogs, revived from cardiac arrest and maintained 5 hours during the postarrest period, were analyzed. They were divided into 3 groups. Animals in Group I (n = 8) had an arrest of 8–11 minutes and those in Group II (n = 12) had an arrest of 12–16 minutes. Animals in Group III (n = 12) had an arrest of 12–16 minutes followed by treatment with a high dose of 40,000 molecular weight dextran, with an initial dose of 1 g/kg at a concentration of 10% in normal saline. Infusion of this drug was instituted immediately after recovery from cardiac arrest. A maintenance dose of 10 mg/kg/min dextran 40 was then given during the 5 hours of the recovery period. Three animals with arrest of 12 minutes were evaluated for postarrest hyperemia. They were followed up to 1 hour after revival and received no treatment.

Details of Surgery, Arrest and Defibrillation

Dogs weighing 15–30 kg were anesthetized with 25–30 mg/kg sodium pentobarbital i.v., intubated and maintained with intermittent positive pressure ventilation (IPPV) using a Harvard respirator at approximately 20 ml/kg stroke volume. The rate of ventilation and percentage oxygen content of the inspired air were varied to maintain PaO2 equal to 100–300 mm Hg; PaCO2 equal to 30–40 mm Hg; and pH equal to 7.35–7.45. Blood gas measurements were made using a Corning Blood Gas Analyzer (Model 165). Before arrest, blood gases were measured repeatedly until they were stable. The first blood gases were measured within 20 minutes of revival and every 15 minutes thereafter until stable, then every half hour during the recovery period. Catheters were placed in: 1) the femoral artery for systemic blood pressure monitoring; 2) the femoral veins for venous pressure monitoring and drug infusion; 3) the aorta via the second femoral artery for reference blood sampling of radioactively labeled microspheres and blood gas samples. Rectal temperature was maintained at 37.5°C. All pressure and ECG measurements were recorded on an 8 channel Beckman Dynograph (Type RM).

A left lateral incision was made to expose the dog’s
heart, the pericardium opened and the left atrial appendage catheterized. This catheter was used for injection of the radioactively-labeled microspheres and for hydration maintenance with a normal saline drip.

At the end of surgery a 1% procaine solution was used to infiltrate the wounds. Additional doses of pentobarbital were given as required. The dogs were immobilized with gallamine triethiodide (Flaxedil, 10 mg i.v.).

Cardiac arrest was obtained using an AC fibrillator at approximately 2-3 volts. In Group I (8-11 minute arrests), the dogs were resuscitated with cardiac massage at approximately 90/min for 1-2 minutes followed by DC defibrillation (20-40 joules) by means of paddles placed directly on the myocardium. In order to increase the revival rate in Groups II and III (12-16 minute arrests), the resuscitation procedures were modified as follows: the ascending aorta was clamped after the arrest and a gentle manual cardiac massage was continuously applied for 11 minutes, then the clamp was removed and the massage rate was increased to approximately 90/min for one minute. This was followed by DC defibrillation. The period from the beginning of fibrillation to the cardiac response to defibrillation was considered as the period of arrest. During rapid cardiac massage, the systemic arterial pressure was usually elevated. However, a 0.25 ml bolus of intravenously injected metaraminol bitartrate solution was often necessary to elevate the pressure to 50-75 mm Hg before defibrillation. Our previous experience revealed that for a higher successful revival rate it was important to elevate the systemic arterial pressure before defibrillation. A total of 20-30 ml of sodium bicarbonate was injected intravenously during arrest and resuscitative periods. Lidocaine (1%, i.v.) was administered when necessary to control premature ventricular contractions (pvc) during the recovery period.

In Group III, 1 g/kg of dextran 40 was infused immediately after revival. Dextran was used at a maintenance dose of 10 mg/kg/min during the 5 hour recovery period. After infusion of dextran, if elevated venous pressure had not begun to decrease within 10 minutes, arterial blood equal or greater in volume to the aorta was clamped after the arrest and a gentle manual cardiac massage was continuously applied for 11 minutes, then the clamp was removed and the massage rate was increased to approximately 90/min for one minute. This was followed by DC defibrillation. The period from the beginning of fibrillation to the cardiac response to defibrillation was considered as the period of arrest. During rapid cardiac massage, the systemic arterial pressure was usually elevated. However, a 0.25 ml bolus of intravenously injected metaraminol bitartrate solution was often necessary to elevate the pressure to 50-75 mm Hg before defibrillation. Our previous experience revealed that for a higher successful revival rate it was important to elevate the systemic arterial pressure before defibrillation. A total of 20-30 ml of sodium bicarbonate was injected intravenously during arrest and resuscitative periods. Lidocaine (1%, i.v.) was administered when necessary to control premature ventricular contractions (pvc) during the recovery period.

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Cortical EEG and regional cerebral blood flow were monitored.

EEG

To record cortical EEG activity, the skull was exposed via a midline incision, and the muscles retracted laterally. Holes were then drilled (using an Emesco Dental Drill Model #90W) in the skull for placing electrodes without penetrating the dura mater. EEG activity was monitored in the right and left frontal, occipital and temporo-parietal regions using a bipolar technique. EEG recordings were obtained using a Grass electroencephalogram (Model #11ID). The EEGs were evaluated every half hour during the 5 hours recovery period. The pattern of recovery was noted and the score developed based on the sequential changes observed in the EEGs. The EEGs were then re-evaluated and scored without knowledge of the experimental group and the duration of flat EEG after the arrest was tabulated. This scoring system is summarized as follows: 5 = normal, 4 = increased slowing, 3 = prominent spindle bursts, 2 = burst suppression without electrical silence, 1 = burst suppression with apparent electrical silence, 0 = flat EEG (electrical silence).

Blood Flow Determinations

Cerebral blood flow was determined using three stock suspensions of microspheres (3M, Minnesota) labeled with Sr85, Ce141, and Yb169, respectively. The microspheres, of a nominal 15 μm diameter, were presuspended in normal saline. On the day of the experiment, the stock suspensions were shaken vigorously and 500-600 microliters drawn up in heparinized 3 ml plastic syringes and diluted to 2.2 ml with normal saline. The radioactivity in the injection syringes was then counted before and after injection using a 2-inch sodium iodide crystal detector (Ortec, Model 276) to determine the actual amount of isotope injected.

Injection of the microspheres was accomplished via the left atrial appendage catheter over 10 to 15 sec. The catheter was then flushed 2-3 times with normal saline to ensure complete microsphere injection. Simultaneously with microsphere injection, a known volume of blood was withdrawn from the aorta over a known time interval; this information was then used in calculating cardiac output and blood flow to tissues. Microsphere injections were made: 1) as soon as the animal was stable following surgery (0 hours or baseline), 2) 3 hours, and 3) 5 hours later. Cardiac arrest was induced within a few minutes of baseline injection. Three animals with arrests of 12 minutes were evaluated for early postarrest hyperemia by injection of isotope at baseline and at 2 times during the first 60 minutes after arrest.

Animals were sacrificed by an intravenous injection of saturated potassium chloride, and the brain removed as rapidly as possible. Grey matter and white matter samples (0.5 to 2 g) were taken from the temporo-parietal, occipital and frontal lobes of the brain and from the cerebellum. Additional brain tissue was sampled from the basal ganglion, thalamus, brain stem and hippocampus for blood flow studies.

Tissue samples, blood samples, and standards were counted in a Packard Tri-Carb Gamma Counter for 2 minutes each, with each isotope counted in duplicate. The standards for each isotope were counted in the Packard Gamma Counter and with the Ortec detector to provide a calibration between the 2 instruments so that pre- and postinjection syringe activity could be mathematically converted to equivalent Packard counts.

At the time of sacrifice, all tissue samples contained all 3 isotopes. Since the gamma energy spectra of
these isotopes overlap to some extent, the contribution (in counts per minute) of each isotope to the total activity of each of the counting windows had to be calculated by solving simultaneous equations. Dividing these values by tissue weight (in grams) and by total activity (in counts per minute) resulted in absolute blood flows in ml/gram/min. The mathematical expressions for calculating cardiac output and cerebral blood flows have been published elsewhere.19 All values are given as mean ± SEM unless specified otherwise.

Results

Hematocrit (Hct) and Serum Osmolality (Table I)

In Group II animals Hct increased during the postarrest maintenance period. In Group III animals the Hct remained the same.

The differences in Hct between the 2 groups during the postarrest period and between the postarrest period and baseline in Group II were both significant (p < 0.05). The increase in Hct was analyzed in those animals with poor or no-recovery and in those with good EEG recovery in Group II animals. There was no difference noted between these animals.

In the treated animals, Group III, blood (200-300 ml) equal or greater than the infusion volume of the dextran solution was removed to avoid overload of fluid, which often produced an increase in venous pressure and could produce pulmonary edema. The infusion dose, however, made hemorrhage a problem during the recovery period. In fact, a few dogs died within 3 hours of the insult as a result of continuous bleeding from their surgical wounds.

Serum osmolality increased in both Groups II and III and more in the latter after the arrest period. The increase was significant for Group III and was only significant at ½ and 3 hours post arrest for Group II (p < 0.05). Increase in serum osmolality in Group II may reflect the increase in tissue osmolality resulting from ischemia and anaerobic glycolysis while in Group III it was due partially to the effect of dextran administration.

Cardiac Output and Blood Pressure

At 3 and 5 hours postarrest, cardiac output in Group I was 54 ± 8% and 53 ± 8% of the baseline. Cardiac output was 78.2 ± 19.3% and 55.7 ± 14.6% respectively of the baseline in Group II animals, and 85.2 ± 18.9% and 51.8 ± 11.9% of the baseline in Group III. The insignificant decrease of cardiac output at 3 hours in Group II and III animals was due to different resuscitation procedures used in these two groups of animals. The decrease in cardiac output was significant both at 3 and 5 hours for Group I and at 5 hours for Groups II and III animals.

Except in animals demonstrating early hypertension, the arterial pressure deviated less than 20% from the baseline level in all groups. In Group I, a small dose (0.1 to 0.25 ml) of metaraminal bitartrate solution was needed in 3 animals to maintain the blood pressure during 5 hours postarrest. Three animals in Group II and two animals in Group III also received an injection of metaraminal bitartrate intravenously during the postarrest period. The blood pressure at baseline, 3 and 5 hours postarrest for Group I was 120.6 mm Hg ± 5.9, 117.5 mm Hg ± 5.7 and 113.8 ± 4.6 respectively, for Group II it was 115.9 ± 3.2, 111.8 ± 2.6, 104.0 ± 2.6 mm Hg and for Group III it was 116.3 ± 4.3, 110 ± 4.7, 100.9 ± 3.9 mm Hg respectively. Except in Group I, the decrease of blood pressure at 5 hours postarrest was significant from baseline both for Groups II and III (p < 0.05).

In general, the blood pressure exceeded prearrest levels within 30 seconds of the end of cardiac arrest. The postarrest mean arterial pressure sometimes exceeded 200 mm Hg with an average of 180 mm Hg ± 13.8. The period of elevated arterial pressure (that is, mean arterial pressure greater than 20% of baseline) lasted from 2 to 40 minutes with a mean of 13.4 ± 3 min. In Group I, although metaraminal bitartrate was not used during arrest, postarrest hypertension occurred in 4 animals. Postarrest hypertension occurred in 7 animals in Group II (12 animals) and in 4 in Group III (12 animals).

Postarrest Hyperemia

Cerebral blood flow was measured repeatedly during the first hour in 3 animals with 12 minutes of arrest. All showed evidence of postarrest hyperemia with a peak occurring at 10 minutes for grey matter flow and 10 and 30 minutes for white matter flow (fig. 1). The percentage increase in flow was higher and longer in duration in white matter than in grey matter. Two (No. 2 and 3) of these animals had no evidence of postarrest hypertension and demonstrated a smaller increase in grey matter flow.

EEG

The pattern of recovery of EEG following the arrest was as follows: initially, there were prolonged periods...
of apparent electrical silence and then very low voltage burst activity was observed. Following this, high voltage bursts of 4–6 Hz activity separated by 2–5 seconds of apparent electrical silence was seen. These bursts then became higher voltage and reached the frequency of 8 Hz. Between these 2 seconds of burst activity low voltage theta and delta activity was apparent. Burst activity then became more frequent and longer in duration and there was less marked suppression between bursts of moderate voltage theta and delta activity. With continuous improvement the pattern of bursts of 8–10 Hz activity became much less prominent. There was also superimposition of theta and low frequency beta activity. Finally, the EEG became indistinguishable from control with a relatively even mixture of 3–4, 8–10, and 12–16 per second activity.

In Groups I and III the EEG returned to control patterns sooner (see fig. 2, table 3) (duration of flat EEG) and with better quality than Group II (EEG score during 5 hour period) (fig. 3, table 3). The duration of a flat EEG in Group I was 31.9 ± 6.5 min, 59.5 ± 10.8 min in Group II and in Group III, 46.9 ± 4.8 min. The EEG pattern during the recovery period in the short arrested group (Group I) showed a gradual recovery while in Group II it demonstrated a bimodal population distribution. Six animals had no or poor recovery while the 5 had a recovery pattern similar to that in Group I. In Group III the EEG recovered much faster than in Group II, the average EEG score at 5 hours was significantly higher ($p < 0.03$ with Mann-Whitney U test) (fig. 4 and table 3). The average score at 5 hours postinsult for Group I was 4.0 ± 0.8 (SD) and for Group II and III was 1.7 ± 1.5 (SD) and 3.09 ± 1.0 (SD) respectively. The duration of a flat EEG and the score at 5 hours post-

| Table 2 | Comparison of Duration of Flat EEG (minutes), EEG Score at 5 Hours Postarrest and Blood Flow Changes at 5 Hours Postarrest Between Animals With or Without Postarrest Transient Hypertension Among the 3 Groups. |
|---------|-------------------------------------------------|-----------------|-----------------|
| Group I | Duration of flat EEG min. ± SEM         EEG score at 5 hrs ± SD | Blood flow at 5 hrs ± SEM |
| PA Hypertension (N = 3) | 37.3 ± 16.3 | 4.3 ± 0.6 | 56.7% ± 5.3 |
| Nonhypertension (N = 3) | 21.6 ± 4.4 | 4.0 ± 1 | 78% ± 15.9 |
| Group II | PA Hypertension (N = 7) | 56 ± 13.7 | 2.0 ± 1.6 | 51.5% ± 5.9 |
| Nonhypertension (N = 4) | 65.5 ± 19.8 | 1.3 ± 1.5 | 51.7% ± 3.7 |
| Group III | PA Hypertension (N = 7) | 49.1 ± 5.9 | 2.9 ± 1.2 | 58% ± 11.6 |
| Nonhypertension (N = 4) | 43 ± 17.4 | 3.5 ± 0.6 | 99.7% ± 35 |

PA = postarrest.
Results of the Study Among the Three Groups

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*Probability that groups are same <0.01 — unpaired Student’s t-test.
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N = number of cases.

Discussion

The effect of cardiac arrest on a number of physiologic variables in this model has been reported previously. The variables of major interest are regional cerebral blood flow as measured with 15 μ spheres, and the EEG. In Group I animals, although there was a marked decrease in the regional cerebral blood flow, there was good recovery of the EEG. Because of the good recovery of the EEG, we thought that a more severe insult would be necessary to evaluate the effects of therapy. In Group II following the arrest there was a significant reduction of flow in cortical gray matter and the hippocampus associated with persistent, severe EEG abnormalities.

Under normal conditions the EEG frequency and cortical cerebral blood flow are closely related to the cerebral metabolic rate. With cerebral hypoxia the correlation between EEG frequency and CBF ceases due to impairment of cerebral blood flow auto-regulation during hypoxia. In this study, except during the postarrest hyperemic period, the correlation of EEG frequency and CBF appeared to exist at 3 and 5 hours postarrest in all groups of animals. The CSF potassium and pH were normal at 5 hours postarrest which was in contrast to the results of others. Nemoto et al. observed that in animals with 15 minutes of global ischemia the cerebrospinal fluid was still acidic 6 hours postischemia, suggesting the existence of vasoparalysis.

Cardiac output was significantly lower than baseline in all groups including the animals with the chest opened but without cardiac arrest. In the latter group the cerebral blood flows were the same as baseline. Even though systemic mean blood pressures were significantly lower than baseline at 5 hours postarrest in both Groups II and III (p < 0.05) they were still in the autoregulatory range. Furthermore, blood gases were maintained at physiologic levels in this study, and thus the systemic hemodynamic changes should not affect local cerebral perfusion.

Table 3 Results of the Study Among the Three Groups

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GROUP I: 8-12 MINUTE ARREST

GROUP II: 12-16 MINUTE ARREST

GROUP III: 12-16 MINUTE ARREST WITH DEXTRAN TREATMENT

FIGURE 4. Diagram showing EEG score obtained every half hour during the 5 hour post arrest period. A — for Group I, 8-12 min arrest, B — for Group II, 12-16 min arrest, C — for Group III, 12-16 min arrest with dextran treatment.

Improvement of cerebral circulation at the microvascular level after infusion of low molecular weight dextran is thought to be related to either the rapid increase in plasma volume with resultant lowering of Hct and reduction in blood viscosity,15,29 or to a direct effect on the RBC which increases its negativity and reduces the tendency to cellular aggregation.29 Using a large infusion dose immediately following recovery from arrest of more than 12 minutes, hypothetically would reduce Hct and blood viscosity and increase osmolality and, therefore, should reverse or prevent perfusion abnormalities.

CHANGES OF BLOOD FLOW IN GREY MATTER AREA FOLLOWING CARDIAC ARREST

ARREST OF 8-11 MIN
ARREST OF 12-16 MIN
ARREST OF 12-16 MIN WITH DEXTRAN TREATMENT
MEAN ± SEM

BLOOD FLOW % OF BASELINE

3 HR
5 HR

FIGURE 5. Histogram showing changes of blood flow in grey matter at 5 hours after revival from cardiac arrest among the 3 groups.

Immediately after reperfusion Cantu et al.4 observed impaired perfusion using carbon black suspension, which persisted for 2 hours after reperfusion but improved with time. Our previous study had similar results.26 In the present study, however, 3 animals, in which early measurements of CBF were made, had hyperemia during the first 30 minutes after reperfusion. It is important to recognize differences between the techniques. The carbon black technique demonstrates small areas of no perfusion, and, by contrast, the microsphere technique may average a small area of no perfusion with a larger surrounding area of hyperemia, so that the average flow will indicate hyperemia. Therefore, the observation of early hyperemia in 3 animals in this study does not imply the absence of areas of “no reflow.”

An improvement of the “no reflow” postischemic circulatory disorder has been achieved by raising the systemic blood pressure,4,8 by administering hypertonic agents,3,4 by hemodilution4,58 or by rinsing the brain vessels with isotonic solutions.44 In this study, one of 3 animals with hyperemia in the early postarrest period was hypertensive; the hyperemia in this animal was greater than in the other 2, suggesting that impaired cerebral autoregulation with vasodilatation, possibly secondary to lactic acidosis, was responsible2,15>22 At 3 and 5 hours early hypertension did not correlate with good outcome either in terms of the EEG or CBF. Therefore, although early hypertension seemed to increase postischemic hyperemia and to decrease the amount of tissue not perfused initially,4,8 it was not necessarily beneficial in the long run. This leads directly to the consideration of other factors.

Narrowing of capillary lumina caused by swelling of endothelial and perivascular cells following global ischemia or cerebral hypoxia has been observed by many investigators.1,5,17,30,34 Recently, Fischer and Ames9 have suggested that changes in blood viscosity might underlie the “no reflow” phenomena.10 They observed that a moderate degree of perivascular cell swelling was not sufficient to interrupt passage of normal red cells and did not find evidence of sufficient cell swelling or bleb formation to lead to luminal collapse. In this study, the observed increase in Hct in the control animals (Group II) indicated that there was a shift of plasma contents from intravascular to extravascular space causing hemoconcentration and hyper-
viscosity. The transient increase in serum osmolality in Group II may reflect the increase in tissue osmolality resulting from ischemia and anaerobic glycolysis. If capillary narrowing does play a role in microvascular deterioration then hemodilution and prevention of cellular aggregates, as occurs with dextran, would be beneficial in minimizing poor flow in narrow capillaries. The direct effect of increased plasma oncotic pressure and decreased intravascular pressure would be to minimize tissue swelling and, therefore, minimize delayed capillary narrowing. If the latter were so, it might explain the lack of long-term beneficial effect of early postarrest hypertension even though its immediate effect might be to overcome stagnant flow.

Also, if the capillary becomes flow-limiting, it might explain the relative lack of CBF responsiveness to CO2 observed by Nemoto et al.

The functional importance of microthrombi has been questioned because it has been speculated that irreversible brain damage has already occurred before the microthrombi developed. The work of Crowell, supplemented with the results of this study as well as extensive work by others, seems to indicate that treatment delivered after a severe ischemic insult may be beneficial and that this benefit may be derived from prevention or lysis of microthrombi. More specific studies to investigate the role of microthrombus formation are in progress.

In conclusion, there are a number of mechanisms by which dextran may operate to improve flow immediately after an ischemic insult and prevent delayed deterioration of flow. This study indicates that dextran 40 treatment improves brain function following cardiac arrest and that this effect may be mediated through changes in the microcirculation.

Acknowledgment

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References

2. Betz E, Kozak R: Der Einfluss der Wasserstoffionen-konzentration der Gehirnrinde auf die Regulation der corticalen Durchblutung. Pflegers Arch 293: 56-67, 1967
Cerebral Oxygen Consumption and Blood Flow in Hypoxia: Influence of Sympathoadrenal Activation

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SUMMARY The effect of hypoxia (reduction of arterial Po2 to 26–28 mm Hg) on cerebral blood flow (CBF) and cerebral oxygen consumption (CMRO2) was studied in paralyzed and artificially ventilated rats, using a CBF technique of improved accuracy at high flow rates. Results obtained on animals maintained on 70% N2O unexpectedly showed that hypoxia of this severity is accompanied by an increase in CMRO2, and they indicated that 2 different mechanisms are involved, both related to catecholamine metabolism. In one breed of Wistar rats studied, hypoxia was accompanied by a 6-fold increase in CBF and by an increase in CMRO2 to 180% of control. Prior removal of the adrenal glands curtailed the increase in CBF (400% of control) and CMRO2 (125% of control). The excessive increase in CMRO2 (to 180% of control) did not occur in another breed of Wistar rats. However, since infusion of adrenaline in normoxic animals gave rise to a doubling of CMRO2, it is concluded that, at least under some circumstances, circulating catecholamines can increase oxygen consumption in the hypoxic brain. In the second breed of rats studied, hypoxia was consistently accompanied by a 20–30% increase in CMRO2 which was unaffected by prior adrenalectomy. However, since infusion of adrenaline in normoxic animals gave rise to a doubling of CMRO2, it is concluded that, at least under some circumstances, circulating catecholamines can increase oxygen consumption in the hypoxic brain. In the second breed of rats studied, hypoxia was consistently accompanied by a 20–30% increase in CMRO2 which was unaffected by prior adrenalectomy. However, since infusion of adrenaline in normoxic animals gave rise to a doubling of CMRO2, it is concluded that, at least under some circumstances, circulating catecholamines can increase oxygen consumption in the hypoxic brain. In the second breed of rats studied, hypoxia was consistently accompanied by a 20–30% increase in CMRO2 which was unaffected by prior adrenalectomy. However, since infusion of adrenaline in normoxic animals gave rise to a doubling of CMRO2, it is concluded that, at least under some circumstances, circulating catecholamines can increase oxygen consumption in the hypoxic brain.

RECENT RESULTS from this laboratory showed that when the nitrous oxide supply was withdrawn from paralyzed and artificially ventilated rats there was a pronounced increase in cerebral metabolic rate for oxygen (CMRO2) and cerebral blood flow (CBF), which could be blocked by previous adrenalectomy, or by administration of propranolol.1 It was tentatively concluded that the increase in CMRO2 (and CBF) was a response to immobilization stress, mediated by circulating catecholamines.

In the course of a study of cerebral metabolic responses to hypoxia (reduction of arterial Po2 to 25–30 mm Hg) we unexpectedly found that CMRO2 rose. Assuming that circulatory catecholamines were responsible, we undertook an extensive study of the effects of hypoxia on CBF and CMRO2 in non-adrenalectomized and adrenalectomized rats, using a CBF method of sufficient accuracy to resolve differences in CBF even at high flow rates. It will be shown that in one breed of rats studied, reduction of Po2 was accompanied by an increase in CMRO2 to almost 200 percent of control, most of which was prevented by prior removal of the adrenal glands. However, in another breed of hypoxic rats maintained on 70% N2O, whether adrenalectomized or not, there was a 20–30% increase in CMRO2. This increase was prevented by administration of diazepam. It is tentatively concluded that the increase was elicited by increased activity in cerebral catecholaminergic pathways. The conclusion is supported by parallel studies showing that a similar increase in CMR02 occurs in hypercapnia, which is blocked both by diazepam and propranolol.

Methods

All experiments were performed on male S.P.F. Wistar rats (290–375 g). During the course of the study, the supplier (Møllegaard, Copenhagen) started breeding a new colony of Wistar rats. Since the results obtained on these breeds differed, they will be described separately. Rats from the original breed constitute series A, from the second, series B and C.

Operative, Anesthetic and Sampling Techniques

Series A. Anesthesia was induced with halothane (2–3%). After they became unresponsive, the animals were tracheotomized and connected to a respirator.
Effect of dextran on cerebral function and blood after cardiac arrest. An experimental study on the dog.

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