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Regional Cerebral Blood Flows in Endotoxin Shock with Methylprednisolone Treatment (39940)

THOMAS E. EMERSON, JR., AND WILLIAM J. BRYAN

Department of Physiology, Michigan State University, East Lansing, Michigan 48824

Introduction. We have reported previously in this journal that *Escherichia coli* endotoxin shock in the dog is associated with severe decreases in blood flows in the pons, medulla, hypothalamus, thalamus, cortex, and pituitary (1). These findings agree with earlier studies from this laboratory which demonstrate 52–63% decreases in cerebral venous outflow from the confluens of the sinuses during 4 hr of shock in the dog (2, 3).

Since it has been suggested that corticosteroids are beneficial during circulatory shock (4–9), the current study was undertaken to determine whether the steroid methylprednisolone could prevent or ameliorate the observed changes in regional cerebral blood flows during endotoxin shock.

Methods. Mongrel dogs of either sex, weighing 14 ± 3 kg, were antesthetized with sodium pentobarbital (30 mg/kg). An endotracheal tube was inserted and animals were respired with a positive pressure respirator. Pressure recordings were made using Statham pressure transducers connected to a Sanborn direct-writing recorder. Polyethylene cannulae were placed into the right femoral artery (for measurement of systemic arterial pressure), into the aorta through the left femoral artery (for withdrawal of reference blood sample after each microsphere injection), into the left ventricle via the left common carotid artery (for microsphere injection), and into the femoral vein (for infusion of endotoxin and drug administration). Regional cerebral blood flows were calculated using the radioactive-labeled particle distribution technique, as previously described (1, 10). Microspheres (15 ± 5 μm) labeled with ^{141}Ce, ^{85}Sr, or ^{51}Cr were randomly injected before and at 2 and 4 hr of shock.

Methylprednisolone sodium succinate (30 mg/kg) (Solu-Medrol; Upjohn Co.) were injected iv 15 min before the endotoxin infusion. Supplemental doses were given hourly at 125 mg (approximately 8 mg/kg). Purified *E. coli* endotoxin (1 mg/kg; $\simeq LD_{100}$) was diluted in normal saline to yield a 20-ml suspension and infused iv over a 5-min period. Arterial pressure was supported with iv infusion of saline and dextran. The animal was sacrificed at the end of 4 hr of endotoxin shock. Duplicate 0.5-g brain samples were then taken from the pons, medulla, hypothalamus, thalamus, cortex, cerebellum, and pituitary gland and counted with a Searle γ counter (Model 1185).

Calculations were made for each tissue sample taken. Blood flows were calculated by dividing the cpm per gram of brain tissue by the cpm of the reference blood sample times the withdrawal rate of the reference blood sample.

Regional cerebral vascular resistances were calculated by dividing the arterial pressure at the time of microsphere injection by the appropriate blood flow. The data were analyzed using Student's t test modified for paired replicates. The standard Student's t test was used for comparison of means between the groups. A P value less than 0.05 was considered significant.

Results. Blood flows in seven regions of the brain are represented in Fig. 1. Initial blood flows (ml/min/100 g) in the methylprednisolone-treated dogs averaged (±SE) 9 ± 1.6 in the pons, 14 ± 1.7 in the medulla, 10 ± 1.4 in the hypothalamus, 16 ± 2.2 in the thalamus, 22 ± 1.5 in the cortex, 25 ± 1.8 in the cerebellum, and 118 ± 51.6 in the pituitary gland; arterial blood pressure was 127 ± 6 mm Hg. The significant finding shown in this figure is that, in the methylprednisolone-treated dogs, blood flows in the pons, medulla, hypothalamus, and thalamus either did not change ($P > 0.05$) or actually increased ($P < 0.05$) during 4 hr of endotoxin shock.

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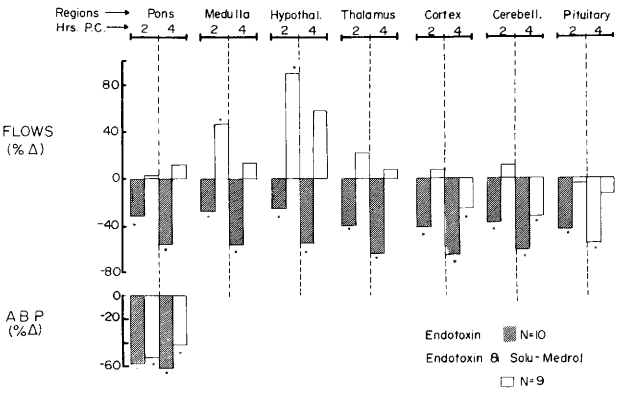

FIG. 1. Percentage change in blood flows (ml/min/100 g) of seven brain regions and arterial blood pressure (ABP) at 2 and 4 hr of endotoxin shock in untreated dogs and dogs treated with methylprednisolone (Solu-Medrol). * = $P < 0.05$ relative to each control value; Hrs. P.C. = hours postcontrol, after endotoxin injection; Hypothal. = hypothalamas; Cerebell. = cerebellum.

On the other hand, blood flows were severely depressed at 2 and 4 hr of shock in corresponding brain regions in untreated dogs ($P < 0.05$). Also, in the methylprednisolone-treated dogs, blood flows in the cortex, cerebellum, and pituitary were not different from control at 2 hr of shock ($P > 0.05$), but flows were moderately decreased in the cortex and cerebellum at the 4th hr of shock ($P < 0.05$). However, the decreases in blood flows in these two regions were much less than those seen in the untreated dogs. The lower bar graph shows that arterial blood pressure was significantly decreased in both treated and untreated groups. However, the average decrease was significantly less in the treated group compared to the untreated group at 4 hr of shock ($P < 0.05$).

Regional cerebral vascular resistances in seven regions of the brain are represented in Fig. 2. Initial resistances (mm Hg/ml/min per 100 g tissue) in the methylprednisolone-treated group averaged (±SE) 22 ± 3.5 in the pons, 12 ± 1.6 in the medulla, 24 ± 5.5 in the hypothalamus, 11 ± 1.5 in the thalamus, 7 ± 0.9 in the cortex, 6 ± 0.4 in the cerebellum, and 2 ± 0.4 in the pituitary. The significant finding shown here is that vascular resistance in each of the seven regions of the brain decreased significantly at 2 and 4 hr in the methylprednisolone-treated dogs ($P < 0.05$). In the untreated dogs, vascular resistance decreased in the pons, medulla, and hypothalamus at 2 and 4 hr of shock, but significantly less than in the treated group ($P < 0.05$); resistance in the other regions is paradoxically not different than control in the untreated group ($P > 0.05$). Again, arterial blood pressure is shown in a lower bar graph.

Discussion. The current study clearly demonstrates that 15-min pretreatment with pharmacological doses of the steroid methylprednisolone, plus supplemental hourly doses, either completely prevents or ameliorates the decreases in blood flow in seven regions of the brain which occur in untreated dogs during 4 hr of endotoxin shock (1). The preservation of regional cerebral blood flows was due largely to decreases in regional cerebral vascular resistances, presumably through some direct or indirect action of the steroid, since blood flows decreased severely in all regions of the brain tested and vascular resistance was either unchanged or insufficiently decreased in dogs which did not receive steroid treatment. An improved systemic arterial blood pressure also helped maintain regional blood flows in the treated dogs.

In addition to maintenance of normal regional cerebral blood flows in the present study, an important effect of methylprednisolone may well be to maintain arterial plasma glucose concentration. We have shown in a preliminary report that dogs treated with methylprednisolone identically to the treatment used in the current study maintained arterial glucose concentration

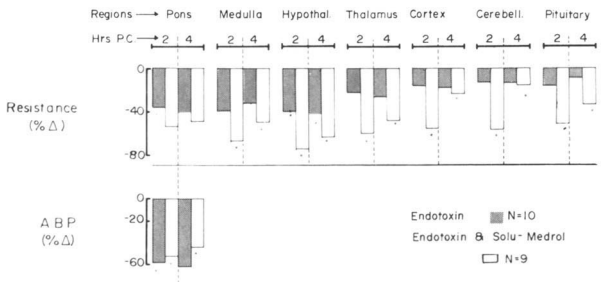

FIG. 2. Percentage change in vascular resistances of seven brain regions and arterial blood pressure at 2 and 4 hr of endotoxin shock in untreated dogs and dogs treated with methylprednisolone (Solu-Medrol); symbols and abbreviations are the same as in Fig. 1.

approximately double the level of untreated dogs during 4 hr of endotoxin shock (11). Also, these steroid-treated dogs did not exhibit changes in cerebral blood flow, brain oxygen uptake, or brain glucose uptake, as opposed to the severe hemodynamic and metabolic disorders which occurred in untreated, endotoxin-shocked dogs (11, 12). This may be an important factor, since data of Hinshaw *et al.* (13) suggest a direct relationship between plasma glucose concentration and survival. They initially noted a progressive decrease in plasma glucose during endotoxin shock in nonsurviving dogs, while dogs in which plasma glucose concentration did not decrease survived. Additional studies demonstrated that plasma glucose concentration also decreases in the subhuman primate during endotoxin shock or live *E. coli* bacteremic shock (14) and in man during gram-negative septic shock (15). Significantly, maintenance of arterial plasma glucose concentration by iv infusion of hypertonic glucose solution prevents death in a significant number of animals during otherwise irreversible endotoxin shock in the dog (13).

The maintenance of regional cerebral blood flows or amelioration of blood flow decreases observed in the present study resulted mainly from decreases in regional cerebral vascular resistances; however, the mechanisms of these decreases is unclear, and could result from a number of factors, including direct and/or indirect actions of the steroid and/or actions of the dextran and saline. Concerning the latter possibility, we have no direct evidence either way, but previous studies suggest that iv fluids alone are not helpful during endotoxin shock (8).

It has been suggested that glucocorticoids act directly on vascular smooth muscle to cause dilation, however, several studies in the literature show that they do not cause active vasodilation during normal conditions or during circulator shock states (5, 8, 9), nor do they exhibit α-adrenergic blocking action (5). However, some of the improvements in cerebral blood flow could be due to prevention of platelet aggregation or prevention of cell disruption and release of vasoconstrictor lysosomal enzymes (5). Since long-term cerebral autoregulation is apparently impaired during endotoxin shock (3), it is possible that methylprednisolone prevents the expected decreases in the cerebral circulation by acting directly or indirectly on cerebral vascular smooth muscle cells, which permits normal long-term autoregulation to occur, although we have no evidence to support this possibility.

Data from the current study demonstrate that methylprednisolone given in large doses before and periodically during endotoxin shock prevents the deleterious changes in cerebral hemodynamics which would otherwise occur. This action may be an additional mechanism by which methylprednisolone provides protection during endotoxin shock.

Summary. It has previously been shown that total and regional cerebral blood flows are severely decreased during endotoxin shock. The effects of methylprednisolone and volume expansion therapy on the regional cerebral blood flows during endotoxin shock in anesthetized dogs are described. Methylprednisolone (Solu-Medrol;

30 mg/kg) was injected iv 15 min prior to infusion of *E. coli* endotoxin (1 mg/kg) and hourly (≃8 mg/kg) for 4 hr of shock. Regional cerebral blood flows were determined using the radioactive-labeled particle distibution technique. In contrast to untreated dogs, treated dogs exhibited no change or an increased blood flow in seven regions of the brain at 2 hr of shock; blood flows in the pons, medulla, hypothalamus, thalamus, and pituitary were not significantly different than control at 4 hr of shock. These data suggest that pretreatment with methylprednisolone, combined with supplemental doses and volume expanders, protects the cerebral circulation during endotoxin shock.

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