Blood–Brain Barrier Breakdown in Reduced Uterine Perfusion Pressure: A Possible Model of Posterior Reversible Encephalopathy Syndrome

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Background: Posterior reversible encephalopathy syndrome (PRES) is a clinical entity characterized by headaches, altered mental status, seizures, and visual disturbances and is associated with white matter vasogenic edema. There are no experimental models to study PRES brain changes. *Methods:* Twenty-eight pregnant Wistar rats were divided into 4 groups of 7: (1) pregnant-control; (2) reduced uterine perfusion pressure (RUPP); (3) invasive blood pressure (IBP); and (4) reduced uterine perfusion pressure plus invasive blood pressure (RUPP-IBP). The RUPP and RUPP-IBP groups were submitted to a reduction of uterine perfusion pressure at pregnancy days 13 to 15. The invasive mean arterial pressure of the IBP and RUPP-IBP groups was measured on day 20. The blood–brain barriers (BBBs) of all groups were analyzed using 2% Evans Blue dye on day 21. *Results:* RUPP rats had higher blood pressures and increased BBB permeability to Evans Blue dye compared with the control animals. Brain staining occurred in 11 of 14 RUPP rats and in none of the control groups ($P < .0001$). *Conclusions:* The physiopathology of PRES remains unclear. Here, we described the use of RUPP rats as a potential model to better comprehend this syndrome. **Key Words:** Posterior reversible encephalopathy syndrome—blood–brain barrier—experimental model—reduction of uterine blood pressure—hypertension.

Posterior reversible encephalopathy syndrome (PRES) is a clinical entity characterized by headaches, altered mental status, seizures, and visual loss. It associated with white matter vasogenic edema on radiologic imaging, predominantly affecting the occipital and parietal lobes of the brain.[1] Numerous factors can trigger the syndrome, most commonly an acute elevation of blood pressure, renal dysfunction, and/or immunosuppressive therapy.[1] Pre-eclampsia (PE) is one of the most common syndromes that is associated with PRES. Other clinical conditions that are associated with PRES are transplantation,[2] cancer and chemotherapy treatment,[3] systemic infections,[4] and acute or chronic renal diseases.[5,6]

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The most characteristic imaging pattern in PRES is the presence of edema involving the white matter of the posterior portions of both cerebral hemispheres, especially the parieto-occipital regions, in a relatively symmetric pattern that spares the calcarine and paramedian parts of the occipital lobes.[1] However, other structures (such as the brain stem, cerebellum, and frontal and temporal lobes) may also be involved. The abnormality primarily affects the subcortical white matter, but the cortex and the basal ganglia may also be involved.[7]

The cause of PRES is unknown. Autoregulatory failure with resultant vasodilation, as observed in hypertensive encephalopathy, is often suggested as the underlying mechanism.[8] On the other hand, vasospasm with ischemic changes is also observed in some patients.[8,9] To our knowledge, a PRES animal model evaluating the underlying mechanisms of this serious syndrome has not yet been established. A well-established model of PE in rats is the reduced uterine perfusion pressure (RUPP), which is associated with arterial hypertension, increased urinary protein excretion, reduced glomerular filtration rate and renal plasma flow, and decreased litter size and pup weight.[10,11]

The blood–brain barrier (BBB) of RUPP animals has not been previously examined. We hypothesize that altered permeability is present and that this model may be proposed to study PRES.

Methods

All the studies were performed in age-matched, timed pregnant Wistar rats. The animals were housed in a temperature-controlled room (23°C) with a 12:12-hour light:dark cycle. All the experimental procedures and protocols executed in this study were approved by the Institutional Animal Care and Ethics Committee from Pontifícia Universidade Católica do Rio Grande do Sul.

Twenty-eight pregnant rats were divided in 4 groups: (1) pregnant-control group (n = 7); (2) RUPP group (n = 7); (3) invasive blood pressure (IBP) group (n = 7); and (4) reduced uterine perfusion pressure plus invasive blood pressure (RUPP-IBP) group (n = 7).

Protocol for RUPP

The animals of the 2 groups (RUPP and RUPP-IBP) were submitted to the intervention to reduce the uterine perfusion pressure.

From day 13 to day 15 of pregnancy, the pregnant rats were anesthetized with 5% of ketamine and 2% of xylazine by intraperitoneal injection. The abdominal cavity was approached via a midline incision. The lower abdominal aorta was exposed, and a silver clip (.2 mm interdiameter) was placed around the aorta above the iliac bifurcation and below the renal arteries as previously described.[10,12,13]

This procedure has been shown to reduce the uterine perfusion pressure in the gravid rat by 40%.[14] The compensation of blood flow to the placenta occurs in pregnant rats by an adaptive increase in the ovarian blood flow. Consequently, a silver clip (.2 mm interdiameter) was also placed on the main uterine branches of both the right and left ovarian arteries.[15]

The RUPP rats in which the clipping procedure resulted in maternal death (n = 1) or total reabsorption (n = 3) of the fetuses were excluded from the study. All the other animals had at least 8 pups.

Protocol for Measurement of Invasive Blood Pressure

The animals of the 2 groups (mean invasive blood pressure and RUPP-IBP) were submitted to the measurement of mean arterial pressure (MAP).

On day 20, an arterial catheter was placed in the carotid artery under anesthesia. On day 21, the measurement of MAP in the conscious rat was performed using a pressure transducer. The arterial pressure was monitored with a pressure transducer connected to the Kananda arterial pressure recording device (Dr. Marcio Flavio Dutra Moraes, Belo Horizonte, Brazil). Kananda is a device that transforms blood pressure measurements via sphygmomanometer into records on a microcomputer in real time.[16]

The measured blood pressure values were transferred to the Excel 2007 software to calculate the MAP of these groups.

Evaluation of the BBB by Evans Blue and Brain Tissue Processing

The BBB permeability was evaluated in all the animals using Evans Blue at day 21. Evans Blue dye (2% wt/vol in .9% NaCl) was intravenously administered (3 mL/kg) via the tail vein at the start of a 3-hour perfusion. At the end of perfusion, the rats were transcardially perfused with 250 mL cold phosphate buffered saline to remove the intravascular Evans Blue dye. The brains were then removed and rapidly frozen in a −20°C freezer.

Brain Evaluation

All the rat brains were macroscopically evaluated by a pathologist who was unaware of the groups. After this analysis, the brains were prepared for a microscopic evaluation using an Olympus CH-30 electronic microscope (Olympus, Tokyo, Japan). The brains were cut into 30 μm coronal sections with a cryostat for microscopic evaluation.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Science version 16.0 (SPSS/IBM–Chicago, IL). The results are presented as the mean and standard deviation. The comparisons between the groups were performed using Student *t* test or the chi-square test.