Title: SECONDARY HYPOTENSIVE INSULTS IN A RAT FOREBRAIN ISCHEMIA MODEL

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Recent work has shown the injured brain to be uniquely sensitive to subsequent hypoperfusion challenges (i.e. secondary insults) [1-2]. This is relevant to anesthesia, since patients with pre-existing neurologic disorders often present for procedures where a significant chance of hypoperfusion exists. Investigations to date have only evaluated secondary insults severe enough to produce EEG isoelectricity. This scenario is not common intraoperatively. More often such challenges are characterized as hypotensive episodes which the healthy brain would be expected to easily tolerate. Accordingly, we have evaluated outcome from global ischemia followed 1 hr later by an episode of either moderate or severe hypotension.

Experiment 1: Thirty-eight fasted Sprague-Dawley male rats were surgically prepared for forebrain ischemia [3].

Group 1: 10 mins forebrain ischemia (bilateral carotid artery occlusion and systemic hypotension) followed 1 hr later by systemic hypotension (MAP = 40±5) lasting 20 mins;

Group 2: 10 mins forebrain ischemia only;

Group 3: Anesthesia only (sham ischemia) followed 1 hr later by 20 mins of MAP=40±5 mmHg.

A 7d survival was allowed. The rats were then neurologically evaluated and histologic injury was assessed in the hippocampus, neocortex, and caudate nucleus.

Experiment 2: Expt 1 repeated, except the secondary insult was enhanced by reducing MAP to 25 mmHg for 20 mins.

Results: There were no physiologic differences except where MAP was purposefully reduced. The EEG became isoelectric during forebrain ischemia and then recovered to an abnormal pattern. However, no further changes were observed during the secondary insult. In Expt 1, hypotension alone resulted in no histologic injury. Ten mins ischemia resulted in 54±20% dead cells in hippocampal CA1. The combination of the primary and secondary insults caused 59±27% dead CA1 neurons. Neurologic differences were not present among the groups. In Expt 2, 10 mins ischemia resulted in 51±19% CA1 injury. The secondary insult alone failed to result in neuronal necrosis while the superimposition of the secondary upon primary insults caused a significant increase ($p<.05$) in histologic injury with 80±17% CA1 neurons dead. Despite this, rats in all three groups were neurologically indistinguishable. Cell death in cortex and caudate was unaffected by either secondary insult.

The post-ischemic phase of delayed hypoperfusion has been shown to be that time when the brain is most sensitive to secondary insults [1]. It has previously been documented that delayed hypoperfusion is evident 1 hr post-ischemia in the ischemia model employed herein. We thus chose that interval to administer the ischemic insult [4]. Despite this, we could identify no gross attenuation of EEG activity, nor enhancement of neurologic/histologic injury when rats were rendered moderately hypotensive (MAP=40 mmHg) during this phase of recovery. Even when the secondary insult was severe (MAP=25 mmHg), only moderate worsening of histologic and no worsening of neurologic outcome were observed. We suggest that secondary insults must generate severe EEG abnormalities to substantially worsen outcome from ischemia.

References: 1. *JCBFM* 7: 773-782, 1987. 2. *Brain Res* 477: 211-224, 1989 3. *Stroke* 20:507-512, 1989. 4. *JCBFM* 4: 425-429, 1984.

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TITLE: Assessment of behavioral outcome following incomplete forebrain ischemia by T-maze performance in rats.

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Hippocampal ablation has been shown to result in an impairment of working (short term) memory whereas reference (long term) memory is not affected. In the present study, a delayed non-match to sample paradigm was used to assess reference and working memory in rats exposed to incomplete forebrain ischemia. Under isoflurane anesthesia, forebrain ischemia was induced in 7 spontaneously hypertensive rats (SHR) by bilateral carotid artery occlusion for 8 minutes combined with hemorrhagic hypotension to 50 mm Hg (ischemic group, I). Preliminary investigations had revealed that ischemia of this duration was sufficient to destroy more than 80% of the cells in the CA1 sector of the hippocampus bilaterally. In 7 additional animals, the carotid arteries were exposed but were not occluded (control group, C). The wounds were then sutured close and the animals were returned to their cages. After a recovery period of 7 days, the animals were started on a food deprivation schedule to maintain their weights at 85-90% of their pre-surgical weight. Prior to behavioral testing, the two groups of animals were indistinguishable with regards to motor function, feeding and grooming behavior. The rats were subsequently trained in a T-maze (10 trials/day) according to the following schedule: 1) T-maze acclimation (3 days). The animals were individually placed in an arm of the maze that was baited with food and allowed to explore the maze for 30 seconds. 2) Reference memory development (5 days). Each trial consisted of two consecutive runs in the maze. With the first run, the animal was forced to enter one arm of the maze. During the second run, access to both arms was provided. However, only the arm opposite to that which the animal had entered on the previous run was baited with food. The animal had to learn to enter the arm opposite to that he had entered during the first run. 3) Working memory testing (3 days). Each trial consisted of two consecutive runs as described above. However, a variable intra-run delay (2, 4, and 6 minutes on consecutive days) was imposed between the two runs. The animal therefore had to remember the arm in which he had entered during the first run for a longer time interval.

Results : Acquisition of the task was delayed in the ischemic group for the first 3 days of maze training (reference memory development) as shown in the table. On the 4 th and 5 th days, both groups had learned the task to the same degree. Performance in the maze with intra-run delays, a test of working memory, was not different between the two groups.

The data suggest that, in this model of incomplete ischemia, task acquisition and reference memory development is delayed. With the T-maze paradigm employed, the dissociation between reference and working memory that has been shown to occur after hippocampal injury using other paradigms was not discernible.

Table: Number of correct runs during maze training.

Day	1	2	3	4	5
C	61	65	63	64	62
I	42*	55 *	51 *	57	62

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