

## CORRESPONDENCE

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### The Evidence That a Serotonergic Mechanism Plays an Important Role in Cryogenic Brain Injury: Are the Results Conclusive?

*To the Editor:*—Recently Archer *et al.*<sup>1</sup> described the influence of cryogenic brain injury on the pharmacodynamics of pentobarbital and the evidence for a serotonergic-mediated reduction of pentobarbital requirement following cryogenic brain injury. Although the study was well-designed and -executed, we believe that the results are not conclusive and that caution should be exercised in the interpretation of the data.

Based on two series of experiments in rats, one pretreated with the antiserotonergic p-chlorophenylalanine (PCPA) and the other without, Archer *et al.* observed that 1) the brain pentobarbital concentration required to prevent response to tail clamp ( $EC_{50}$ ) was significantly decreased by cryogenic injury and 2) pretreatment with PCPA prevented this decrease, thus providing "support for a functional role for 5-hydroxytryptamine in the influence of cold injury on the pharmacodynamics of pentobarbital." Based on the results, we agreed with the first conclusion, but for the second conclusion to be valid, two additional conditions must be fulfilled: 1) PCPA pretreatment alone does not alter the  $EC_{50}$  of pentobarbital, and 2) a significant difference in  $EC_{50}$  exists between the untreated injured group and the PCPA-pretreated injured group (reduced in the former and unchanged in the latter). As shown in figure 2 of Archer *et al.*'s study, the second condition is not met. Although the authors demonstrated that there was no statistically significant difference in pentobarbital  $EC_{50}$  between the injured and uninjured animals following PCPA pretreatment, they did not establish that PCPA alone did not decrease the  $EC_{50}$  of pentobarbital (although this appears to be the case). More importantly, there was no apparent difference in pentobarbital  $EC_{50}$  between the untreated injured animal and the PCPA-pretreated injured animal. Thus, despite lower 5-hydroxytryptamine levels in the PCPA-pretreated animals, the  $EC_{50}$  was not significantly altered. Reanalysis with ANOVA for all four groups followed by a multiple comparison procedure may be more revealing. In addition, because the absence of difference is not proof of equality,  $\beta$  error analysis would also strengthen the arguments.

We recently completed a study<sup>2</sup> on the influence of closed-head injury on minimum alveolar concentration (MAC) of halothane. Although initial results suggest that MAC was decreased by head trauma, a more detailed examination reveals that, unless the rats were very severely injured with a neurologic score equivalent to Glasgow Coma

Scale score of 5 in humans, it was not significantly affected by the injury.

Although in both studies brain injury was inflicted, the results are different. Possible explanations of this difference include the following. 1) The different timing: we studied the MAC for the first 48 h after injury, whereas Archer *et al.*<sup>1</sup> studied it 3 days after the trauma. 2) The different nature of injury: different models—head trauma with weight drop device *versus* cryogenic injury—were used. 3) Different drugs—halothane *versus* pentobarbital—were used. These differences highlight the importance of model and type of injury in both pharmacodynamic studies.

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#### REFERENCES

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2. Shapira Y, Paez A, Lam AM, Pavlin EG: Influence of traumatic head injury on halothane MAC in rats (abstract). *Anesth Analg* 74:S282, 1992

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*In Reply:*—The design of our experiment<sup>1</sup> was to compare the effects of cold injury on  $EC_{50}$  for pentobarbital in untreated animals and in animals pretreated with PCPA to block serotonin biosynthesis. We were advised by our statistical consultant\* that the most appropriate statistical test for this design was two-way ANOVA. This test evaluated the effect of the cryogenic lesion on  $EC_{50}$  in each of the groups and also evaluated the effect of PCPA treatment (insignificant,  $F = 0.013$ ,  $P = 0.91$ ).

\* Brandt R: Personal communication.

In addition, this analysis confirmed a significant difference of the effect of the lesion on  $EC_{50}$  between the untreated and the PCPA-treated groups ( $F = 4.56$ ,  $P = 0.04$ ). This method obviates the necessity of doing a power analysis on the  $EC_{50}$  data for the PCPA-treated group. We believe that these results provide support for a functional role of serotonin in the influence of cold injury on the pharmacodynamics of pentobarbital. We do not claim that the results are conclusive.

With regard to differences between the results reported by Shapira *et al.*<sup>2</sup> and our report, we suggest that the evaluation of anesthesia depth was very different. In a MAC study, the end-point usually is the abolishing of *purposeful* movement. In our study, the end-point was the abolishing of any, including reflex, movement. Differences in  $EC_{50}$