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CORRECTION

Correlation between the anaesthetic effect of halothane and saturable binding in brain

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IN a previous issue of *Nature*, we reported that the anaesthetic effect of halothane correlated with the occupancy of a saturable chemical environment in rat brain[1]. We have extended these observations by examining the equilibration of halothane between cerebral cortical brain slices and anaesthetic-equilibrated buffer, an experimental paradigm in which whole-animal physiology cannot influence brain anaesthetic uptake. These studies showed that brain-slice halothane concentration was, with only minor deviation, a linear function of buffer concentration. This discrepancy between *in vitro* and *in vivo* equilibration studies led us to re-examine *in vivo* uptake of anaesthetic by simultaneously measuring brain and blood halothane concentrations in rats anaesthetized with various inspired concentrations of halothane. These studies showed higher brain and plasma halothane concentrations than those we originally reported (Fig. 1): this results from improved calibration technique and possibly, in plasma, from reduced loss of halothane by volatilization during sample preparation. Brain and blood halothane concentrations were seen to rise in parallel as a function of inspired concentration, and the brain/blood halothane ratio (inset of Fig. 1) was constant over the entire inspired concentration range studied. The observed nonlinear relationship between inspired and blood halothane concentrations was not the result of blood saturation, as *in vitro* halothane/gas partition coefficients (37 °C) were the same (2.78 ± 0.08) at 1% (v/v) and 3% halothane. These data indicate that anaesthetic-induced depression of halothane uptake into blood is predominantly responsible for the apparent saturation of brain observed *in vivo*; the apparent saturation reported earlier[1] is not the result of a limited number of binding sites in brain.

We have also reported the existence of two chemical environments for halothane (and for other volatile anaesthetics) in brain[2], as defined by ^{19}F-NMR spin–spin relaxation behaviour[1]. The two environments are differentially occupied as a function of both inspired anaesthetic concentration and duration of delivery; occupancy of one of these environments (that with a short T_2) correlates with the anaesthetic effect of halothane. In light of our recent findings, it is apparent that occupancy by halothane of the short T_2 environment scales with total brain concentration; this environment is not saturable over the range of concentrations attainable *in vivo*. The other (long T_2) halothane environment represents an increasing proportion of total brain halothane concentration as a function of increasing inspired concentration and duration of anaesthetic administration. The basis for differential occupancy of the two halothane environments is not known, but could be the result of time- and concentration-dependence of either anaesthetic-induced membrane disruption[3] (producing the long T_2) or changes in regional blood-flow distribution (for example, to white and grey matter). Although the physical chemical basis for the ^{19}F-NMR relaxation behaviour of anaesthetics in brain remains unknown, this relaxation behaviour is likely to be pharmacologically relevant, as evidenced by the strong correlation between volatile anaesthetic potency and ^{19}F-NMR T_2 values in brain[2]. We are continuing to investigate the structural basis for and the pharmacological relevance of anaesthetic ^{19}F relaxation behaviour in brain. This letter is submitted to correct the record as regards our previous report[1]. □

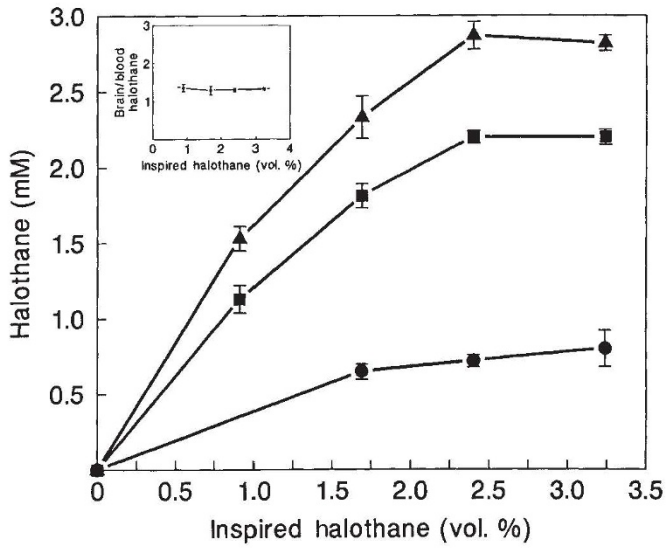

FIG. 1 Brain and blood halothane concentrations simultaneously measured in spontaneously ventilating rats. Rats were allowed to breathe various inspired concentrations of halothane (measured by gas chromatography) for 1 hour. Arterial blood was withdrawn and the animals were decapitated. Blood halothane concentrations (■) were measured by gas chromatography, and brain halothane concentrations (▲) were measured both by gas chromatography and by NMR (ref. 1). Gas chromatography and NMR measurements of brain halothane gave identical results. In parallel experiments, plasma halothane concentrations (●) were measured by gas chromatography. Note that plasma halothane concentrations were reasonably well predicted by our *in vitro* measurement of the rat plasma/gas partition coefficient of ~1.3. The inset shows the brain/blood halothane concentration ratio plotted as a function of inspired concentration. All data are the mean ± s.d. of 3–6 determinations.

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