F-18 Labeled Volatile Anesthetics: Synthesis and in vitro Applications

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Modern surgery would not be feasible without general inhalation anesthetics, but the mechanism of action of these compounds is still controversial. Ever since Meyer and Overton described the correlation between anesthetic potency and hydrophobic partitioning, the accepted theory has been that general anesthetics act by disrupting the static structure or dynamic function of lipid membranes in neurons. However, accumulating evidence suggests that general anesthetics act partly by direct binding to integral membrane proteins. In this context, the current thesis details the development of 18F labeled volatile anesthetics as tools for both in vitro and in vivo anesthetic - protein interaction investigations.

Following the previous pioneering work of our group, 18F labeled volatile anesthetic molecules were synthesized by an isotopic exchange reaction. The 18F for 19F exchange reaction was refined to provide tracers with high radiochemical purity and high specific activity. Both [18F]isoflurane and [18F]halothane were synthesized with radiochemical purities in excess of 10 Ci/mmol.

The synthesis was optimized further by carrying out the exchange reaction in a microwave cavity. The novel cavity was fully characterized and used in the synthesis of the clinical tracer 18F 2-fluorodeoxy glucose. The substitution step of this reaction was accelerated by a factor of five versus a standard heating bath. When the microwave cavity was used for the isotopic exchange reaction, reaction rates were increased by a factor of ten to twenty.

The radiolabeled fluorinated anesthetics were used in two separate in vitro assays to evaluate the binding affinity of volatile anesthetics to bovine serum albumin in solution. The first assay was a simple equilibration technique. This technique was used to determine the dissociation constants for halothane, isoflurane, sevoflurane, and desflurane to bovine serum albumin. Volatile anesthetic - protein binding was also measured by [18F]halothane photoaffinity labeling. The dissociation constant for halothane - BSA binding was measured directly with this technique. In addition, the ability of several other molecules to inhibit [18F]halothane photolabeling was measured. The results show that 18F labeled anesthetics are ideally suited tracers for both in vitro and in vivo anesthetic - protein interaction studies.