Wyandotte Cave was explored by prehistoric Native Americans using hickory bark torches as early as about 3,500 years ago, while mining flint, aragonite, and, perhaps, epsomite as far as 3,000 feet from the entrance. White aragonite was quarried from deposits at the base of what is now called the Pillar of the Constitution in the Senate Chamber; artifacts made from this material have been found at various sites in the Midwest.

The first European exploration was made in 1798 into what was named Epsom Salts Cave (later called Old Cave). Some saltpeter was possibly leached from the cave earth in Old Cave during the War of 1812, but more likely the nitrates were mined from nearby Saltpeter Cave.

Explorers discovered passages in 1850; named New Cave, the cave was opened commercially soon afterward, falsely claiming 23.5 miles of passages. Accurate surveys in the late 1960s proved the known cave to be 5.6 miles long. In 1987, exploration of another nearby cave led to the discovery of its connection with Wyandotte Cave, making the length of the entire cave system 9.2 miles.

Wyandotte Cave contains some of the largest passages and rooms within any cave in Indiana. Rothrock’s Grand Cathedral is the highest room in the cave at 136 ft, also having a length of approximately 330 ft and a width close to 90 ft.

The Wyandotte Cave property was purchased by the state of Indiana in 1966 and declared a National Natural Landmark by the National Park Service in 1972.