The orderly control, coordination, and regulation of a myriad of processes throughout the body are dependent on the uninterrupted functional activity of the brain. The vast array of physical and chemical processes that sustain and comprise cerebral functional activity are largely energy-dependent. The required energy is provided by cerebral energy metabolism, and the brain is metabolically one of the most active organs of the body.

In adult man, for example, in which the brain comprises only 2% of the body weight, it alone accounts for approximately 20% of the total oxygen consumption and maintains a steady rate of energy expenditure of at least 20 watts! (Iversen, 1978). Further, in contrast to most other tissues, which exhibit considerable flexibility with regard to the nature of substrates for energy metabolism, the brain is normally restricted almost exclusively to glucose.

The absolute dependence of brain on glucose is reflected by the fact that endogenous stores of available carbohydrates in this tissue are negligible compared to its rate of oxidation, and, therefore, it has to depend on the continuous replenishment of glucose.
supplies by the cerebral circulation. From circulation, glucose is transported into the brain via the blood-brain-barrier, by a hexose-specific carrier-mediated facilitated transport.

The transport capacity of the carrier is sufficiently high so that the normal influx of glucose is considerably in excess of the need. Thus the rate of cerebral glucose utilization is never limited by the transport of glucose through the blood-brain-barrier, except when the transport itself is limited by restrictions in the delivery of glucose to the brain either by hypoglycemia or cerebral ischaemia.

As brain normally derives all its energy from the aerobic oxidation of glucose, the regulation of glucose utilization is achieved at the reaction sequences subsequent to the transport. The most important reaction sequence for glucose metabolism in the brain is the glycolytic pathway; and the key enzymes of the pathway, namely, hexokinase, phosphofructokinase, and pyruvate kinase, therefore, primarily determine the rate of glucose utilization by the brain (Lowry and Passonneau, 1964; Rolleston and Newsholme, 1967).

Such being the importance of glucose for the brain, it is imperative that the glycolytic enzymes are
so regulated as to enable the brain to adapt promptly and efficiently to alterations in environmental conditions. The present investigations, therefore, were aimed at gaining some insight into the mechanism of regulation of the key glycolytic enzymes, phosphofructokinase and pyruvate kinase, and their role in brain glycolysis under different hormonal conditions.

Insulin and thyroid hormones exert profound effects on the structure and function of the brain, and their role in the regulation of energy metabolism in many tissues is an intricate one. An imbalance in the secretion of either of the hormones may have severe effects on the brain metabolism. Insulin deficiency, e.g., in diabetes, has been known to result in depressed brain energy metabolism, associated with several morphological changes in peripheral nerves. These factors contribute to the development of diabetic neuropathy. Thyroid hormone deficiency, particularly at young age, severely retards structural and functional development of the brain, including its energy metabolism, leading to the well known conditions of cretinism.

Therefore, considering the continuous and large demand of energy by the brain, and the role of phosphofructokinase and pyruvate kinase in the energy
metabolism, it was felt desirable to study the behaviour of the two brain enzymes under different insulin and thyroid status. The aim of the present study was to see how the enzymes adapt themselves and regulate the glycolytic pathway under conditions that are not favourable to the brain energy metabolism.

The activities of phosphofructokinase and pyruvate kinase were followed in different brain regions, namely, cerebral hemispheres, cerebellum and brainstem under conditions of alloxan induced diabetes, hyperinsulinemia, thyroidectomy, and hyperthyroidism. Instead of whole brain tissue it was preferable to take the three discrete brain regions, as it is known that brain, structurally or functionally, is not a homogeneous tissue. Cerebral blood flow, oxygen consumption, and the rate of glucose utilization, all are known to vary widely with the different types of brain cells. Moreover, the effects of insulin and thyroid hormones on brain metabolism is known to be not general, but regionally selective. Besides the brain regions, the heart and liver tissues were also included in the study in order to assess the comparative role of the two glycolytic enzymes under different hormonal conditions.

The changes in enzyme profile during the hormonal conditions was followed in a time sequential
manner. The time period chosen were such as to correspond to short-term as well as long-term influence of the hormones. Further, in order to ascertain the reversibility of the effects of the hormones, the hormone-deficient animals were administered with exogeneous hormones and the enzymes activities under the two conditions were compared.

The activities of phosphofructokinase and pyruvate kinase is known to be regulated by a number of metabolites, e.g., nucleotides, glycolytic and citric acid cycle intermediates, amino acids and various ionic species. Several of these metabolites undergo changes in the brain under different physiological conditions. In order to have a better understanding of the role of these metabolites in the brain metabolism, their effects were tested in vitro on the purified preparations of brain phosphofructokinase and pyruvate kinase. Thus, the second part of the study constitutes purification of the two glycolytic enzymes from the rat brain and their kinetic and regulatory behavior.