PREFACE

Since the middle of this century, a quasi exponential course of progress in the field of biogenic monoamines has been characterised by a close feedback interaction between basic research of the disturbances of amine metabolism and drug development. Considerable literature is available on the effective disorders underlying over and under-production of specific amines. Excessive production leads to untoward display of the biological activities of these amines whenever they are released locally or into the blood, and a deficient production, on the other hand, is registered clinically as abnormal organ function.

The advancement of fundamental knowledge on monoamines greatly stimulated the search for new drugs and in the elucidation of their basic mechanisms. For instance, two findings obtained with drugs were decisive in the 'explosion' of monoamine research, namely, (a) that reserpine, a psychosedative drug, caused a long-lasting marked depletion of 6-hydroxy tryptamine in tissues including brain (Shore et al., 1955; Pletscher et al., 1956), and (b) that monoamine oxidase inhibitor, iproniazid, which increases the monoamines in the brain and counteracted the amine depleting effects of reserpine, improved mental depression in man (Pletscher et al., 1965, 1973).
With further developments in monoamine research, the enzyme monoamine oxidase in brain began to be implicated in several processes such as affective disorders (Jain and Jain, 1973), and aggressive behaviour (Consolo and Valzelli, 1970). One of the important roles of MAO, lately discovered was that it regulates the circulating levels of a number of biogenic amines, which are known to have an inhibitory effect on insulin release.

Thus, it was felt imperative to study the role of monoamine oxidase, and extrapolate the possible inclusion of MAO monoamine system in the pathophysiology of insulin deficient physiological state (experimental diabetes).

The study of Na⁺K⁺ATPase in brain in insulin deficient physiological state was no less important, because this enzyme has been implicated in the regulation of release and uptake of neurotransmitters (Logan and O'Donovan, 1980 a,b) which are known to have an inhibitory effect on insulin secretion.

The monoamine metabolism is disturbed not only during diabetes, but also during thyroid deficient physiological status, and drug induced conditions (Engstrom, 1974; Jansson, 1977).

Thyroid hormones have been observed to increase the catecholamine turnover. Hence the study of monoamine oxidase (responsible for amine degradation) and
the Na\textsuperscript{+}K\textsuperscript{+}ATPase (responsible for amine release and/or uptake) was undertaken in hypo- and hyper-thyroid states.

Administration of 6-aminonicotinamide (6-AN), an antimetabolite of NADP has an indirect effect on the monoamine biosynthesis. 6-AN causes an inhibition of pentose phosphate pathway, thus making the NADPH unavailable for the tetrahydropteridine cofactor of tyrosine hydroxylase, resulting in deranged monoamine synthesis. It was, therefore, essential to study the MAO/Na\textsuperscript{+}K\textsuperscript{+}ATPase system which may reveal the activity patterns of these enzymes, and also the mechanism of how the neurotransmitter monoamine are conserved when their biosynthetic pathway is rendered non-operative.

The molecular mechanistic interpretation of the regulation of monoamine metabolism would gain sufficient grounds, if the in vivo studies could be supplemented with in vitro studies using purified preparations of monoamine oxidase and Na\textsuperscript{+}K\textsuperscript{+}ATPase. It was with this in mind that the monoamine oxidase and Na\textsuperscript{+}K\textsuperscript{+}ATPase in brain were purified.

While probing into the MAO inhibition kinetics by clorgyline and deprenyl (MAO A and MAO B inhibitors respectively), a new type of clorgyline and deprenyl
insensitive MAO was found in the cytosolic fraction. The ineffectiveness of some of the antidepressant drugs may be attributed to this cytosolic MAO, and, therefore, purification of this soluble MAO and comparison of its properties with that of the purified mitochondrial enzyme was planned.

Earlier reports (Lai et al., 1980) have shown that clorgyline and deprenyl inhibit the uptake of catecholamines in the synaptosomes, which can be compared to the high affinity uptake of catecholamines involving the synaptosomal Na⁺K⁺ATPase and ATP breakdown (Logan and O'Donovan, 1980 a,b). These observations lead to the assumption that the uptake might be dependent on the oxidatively deaminated product of catecholamine, which, in turn, has a modulatory effect on Na⁺K⁺ATPase. Moreover, MAO is not an uptake enzyme, and hence should not cause an inhibition in uptake of catecholamine after its inhibition with clorgyline.

Thus, the possible involvement of MAO in the regulation of Na⁺K⁺ATPase in brain was thought to be of relevance. Therefore, the in vitro studies using purified Na⁺K⁺ATPase was carried out, which showed that it could be the catecholamine derived aldehydes which modulate the Na⁺K⁺ATPase activity in brain.
A 'mitochondrial signal hypothesis' is postulated and proposed in the present dissertation, which may explain the uptake mechanism of catecholamines and also the inclusion of MAO/monoamines/Na\(^+\)K\(^+\)ATPase system in the pathophysiology of hormonal and drug induced physiological states.