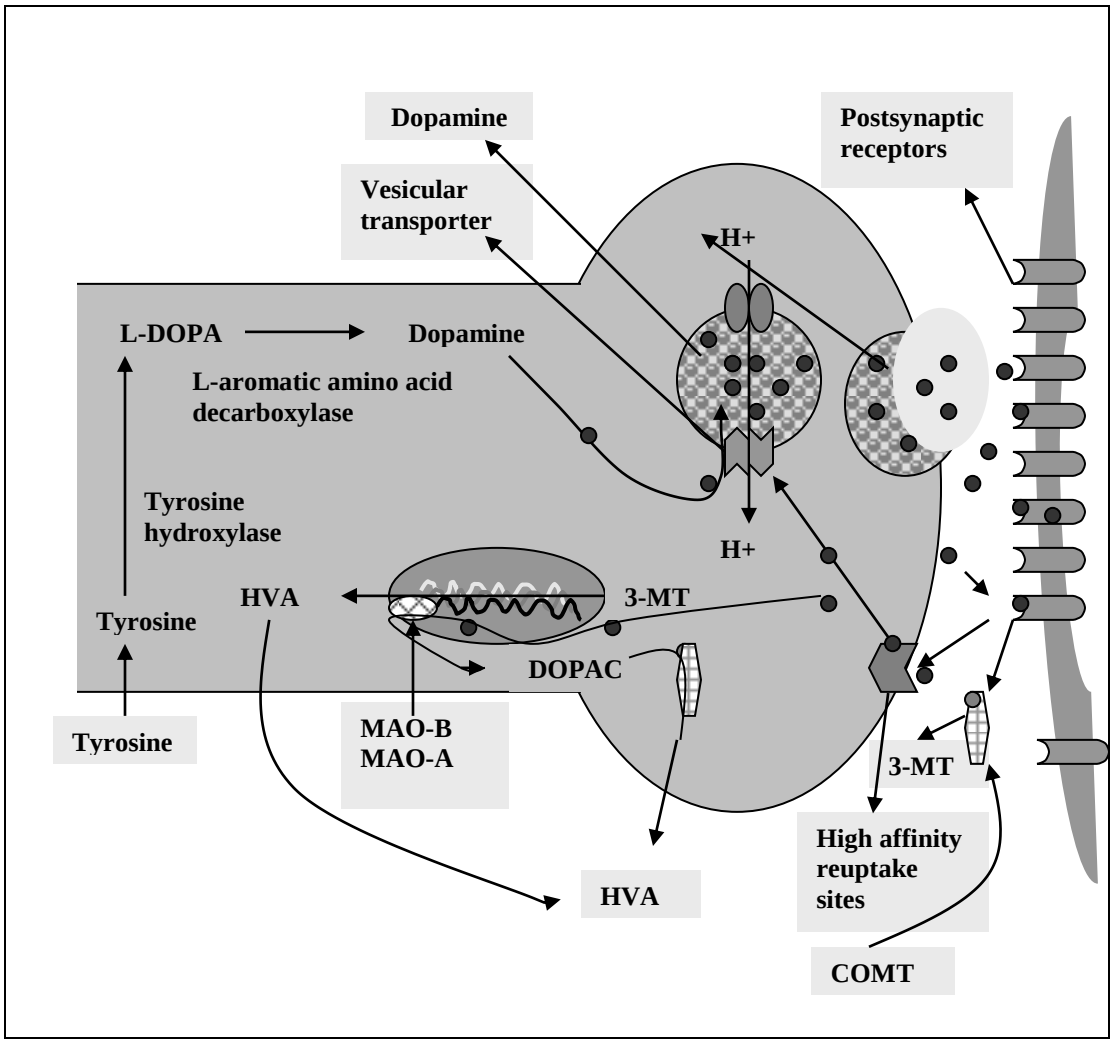
DOPAMINERGIC SYNAPSE



FIG

SCHEMATIC MODEL OF A DOPAMINERGIC SYNAPSE: SHOWING SYNTHESIS, STORAGE, RELEASE, REUPTAKE AND DEGRADATION OF DOPAMINE.

CATECHOLAMINES

The catecholamines belong to a wider group of neurotransmitters called monoamines that is compounds possessing a single amine (-NH_2) group. More specifically catecholamines contain a nucleus of catechol (benzene ring with two adjacent hydroxyl groups and aside chain of ethylamine or one of its derivatives). By far the most important catecholamines are dopamine (DA), noradrenaline (NA) and adrenaline (A).

DOPAMINE

It was not until the late 1950's that DA was recognized as a neurotransmitter. Interest in DA was intensified by the realization that it had an important role in the pathogenesis and treatment of certain brain diseases such as Parkinson's disease and Schizophrenia.

The precursor for all the catecholamines including DA is L-tyrosine an aromatic amino acid derived largely from dietary proteins. Tyrosine is also synthesized in the liver by enzyme phenylalanine hydroxylase. However, this step normally serves as the first step in the degradation and elimination of phenylalanine. A carrier that transports all large neutral amino acids namely, phenylalanine, tyrosine, tryptophan, threonine, leucine, isoleucine, valine and methionine transport tyrosine absorbed in the blood circulation to the brain.

The first step in catecholamines synthesis is the hydroxylation of L-tyrosine to L, 3,4 dihydroxy phenylalanine (L-DOPA). Thjs reaction is catalyzed by the enzyme tyrosine hydroxylase (TH). The enzyme present in the cytoplasm of only catecholaminergic neurons is the rate-limiting enzyme of the biosynthesis. Second step of the biosynthesis involves decarboxylation of L-DOPA by a relatively less specific enzyme L-aromatic aminoacid decarboxylase (L-AADC). As implied by its name the enzyme acts on a variety of L- aromatic aminoa cids besides L-DOPA.

VARIOUS ENZYMES AND OTHER COMPONENTS INVOLVED IN THE SYNTHESIS AND DEGRADATION OF ACETYLCHOLINE

ABBREVIATION	FULL NAME
3-MT	3-METHYL TYRAMINE
DOPAC	DIHYDROXYPHENYL ACETIC ACID
HVA	HOMOVANILLIC ACID
COMT	CARBOXY METHY TRANSFERASE
MAO	MONOAMINE OXIDASE

REGULATION OF CATEHOLAMINE SYNTHESIS

Catecholamine synthesis is regulated by a number of processes, many of which operate via rate limiting enzyme TH. Some of the factors that regulate operate rapidly i.e. within seconds thereby allowing cells to respond to short term need. Other factors operate over long term intervals i.e. hours or days.

ACUTE REGULATION

The activity of TH is acutely regulated by one of the followings;

- AVAILABILITY OF PTERIDINE COFACTOR, TETRAHYDROPTERIDINE (PTH_4):

  The enzyme TH is present in both reduced (TH-H2) and oxidized (TH) form. It is the reduced form that binds tyrosine. Hydroxylation of tyrosine results in the formation of L-DOPA and TH-H2 is converted to TH. TH is reduced by the cofactor PTH_4 that is converted to PTH_2. Catecholamines synthesized in excess bind the cofactor PTH_4. The cofactor is therefore not available to reduce TH in to

TH-H2. A fed back effect on the activity of TH is therefore provided by the excess amounts of catecholamines.

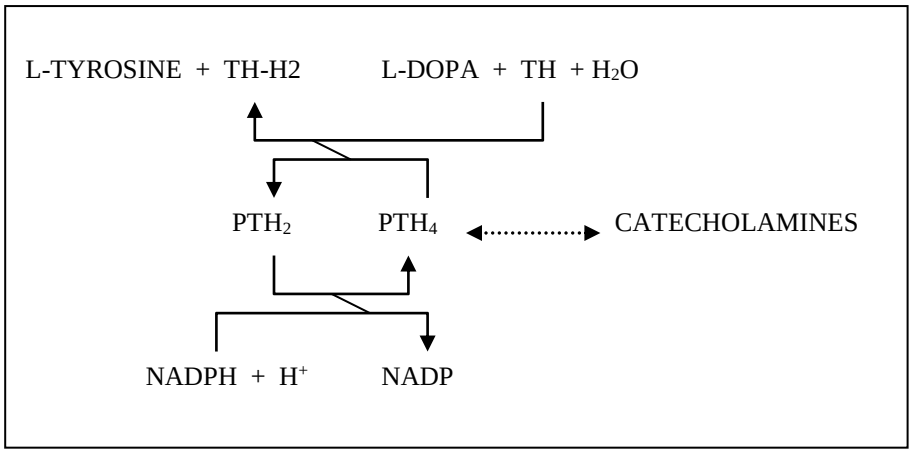
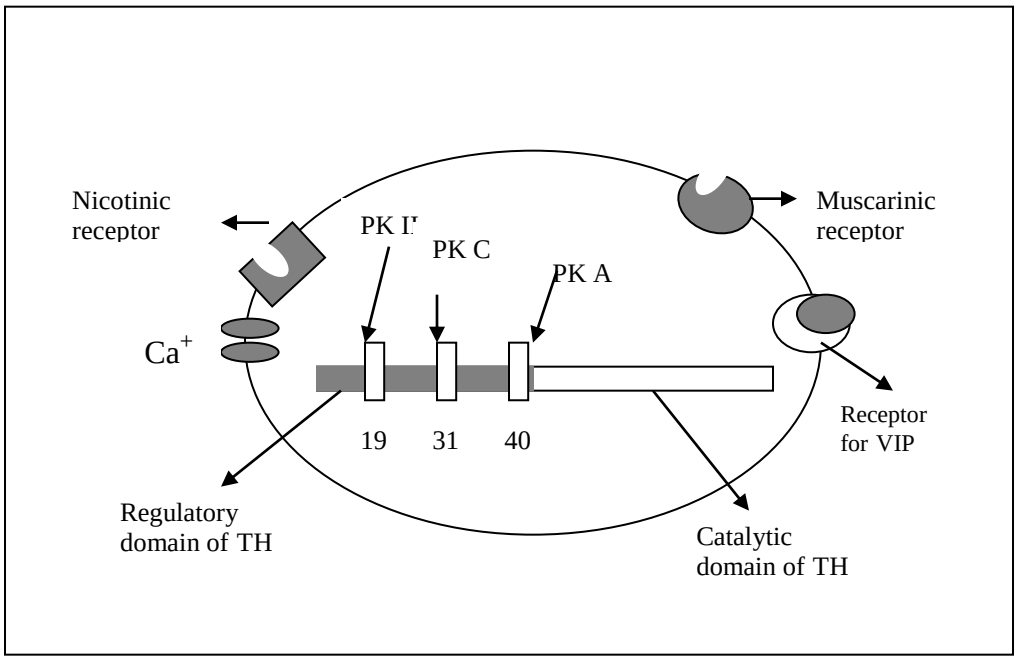


FIG REGULATION OF TH ACTIVITY BY PTH_4 AND CATECHOLAMINES SYNTHESIZED IN EXCESS



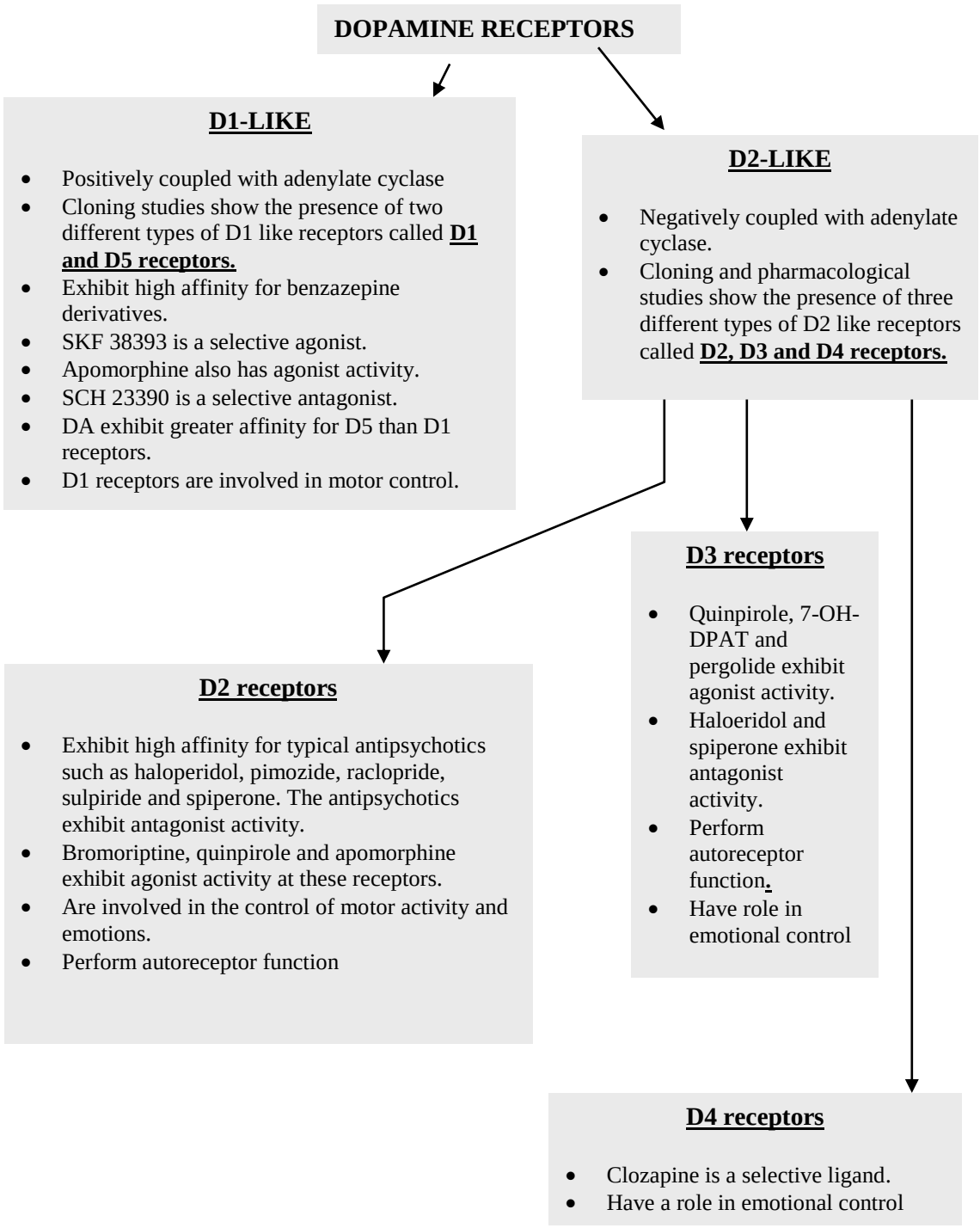
FIG

MECHANISM INVOLVED IN THE PHOSPHORYLATION OF REGULATORY DOMAIN OF TH BY AN INCREASE IN INTRACELLURAL OR Ca^{+2} CAMP CONCENTRATION

TABLE 1

DRUGS ACTING PRESYNAPTICALLY AT A DOPAMINERGIC SYNAPSE

SITE OF ACTION	DRUG	THERAPEUTIC USE
PRECURSOR	TYROSINE	----------
IMMEDIATE PRECURSOR	L-DOPA	Used for the treatment of Parkinson's disease
INHIBITOR OF TYROSINE HYDROXYLASE	α-METYL PARA TYROSINE (AMPT)	----------
INHIBITOR OF L-AROMATIC AMINO ACID DECARBOXYLAE	α-METHYL DOPA HYDRAZINE (CARBIDOPA)	Can not permeate blood brain barriers and along with L-DOPA it is used for the treatment of Parkinson's disease
	3-HYDROXY BENZYL HYDRAZINE (NSD 1015)	----------
STORAGE DESRUPTOR	RESERPINE	Has been used previously fro the treatment of Schizophrenia
RELEASER	AMPHETAMINE	Stimulant and anorectic compound, not used because of addiction
	α–METHYLPHENIDATE	Used in attention deficit disorder in children
REUPTAKE INHIBITOR	BENZTROPINE	Potentiates action of L-DOPA in Parkinson's disease
COMT INHIBITOR	TROPOLINE PYROGALLOL	Could potentiate the availability of systemically administered L-DOPA used for the treatment of Parkinson's disease
INHIBITOR OF MAO-A AND MAO-B	IPRONIAZID ISOCARBOXAZID TRANYLCYPROMINE PHENELZINE	Antidepressants
INHIBITOR OF MAO-A	CLORGYLINE MOCLOBEMIDE	Antidepressants
INHIBITOR OF MAO-B	DEPRENYL	Potentiates effects of L-DOPA in Parkinson's disease
NEUROTOXIN TAKEN UP BY HIGH AFFINITY REUPTAKE SITES	6-HYDROXY DOPAMINE (6-OH-DA)	----------


DOPAMINE RECEPTORS
D1-LIKE
Positively coupled with adenylate cyclase
Cloning studies show the presence of two different types of D1 like receptors called D1 and D5 receptors.
Exhibit high affinity for benzazepine derivatives.
SKF 38393 is a selective agonist.
Apomorphine also has agonist activity.
SCH 23390 is a selective antagonist.
DA exhibit greater affinity for D5 than D1 receptors.
D1 receptors are involved in motor control.
D2-LIKE
Negatively coupled with adenylate cyclase.
Cloning and pharmacological studies show the presence of three different types of D2 like receptors called D2, D3 and D4 receptors.
D3 receptors
Quinpirole, 7-OH-DPAT and pergolide exhibit agonist activity.
Haloeridol and spiperone exhibit antagonist activity.
Perform autoreceptor function.
Have role in emotional control
D2 receptors
Exhibit high affinity for typical antipsychotics such as haloperidol, pimozide, raclopride, sulpiride and spiperone. The antipsychotics exhibit antagonist activity.
Bromoriptine, quinpirole and apomorphine exhibit agonist activity at these receptors.
Are involved in the control of motor activity and emotions.
Perform autoreceptor function
D4 receptors
Clozapine is a selective ligand.
Have a role in emotional control

TABLE

DRUGS ACTING POSTYNAPTICALLY AT A DOPAMINERGIC SYNAPSE

SITE OF ACTION	DRUG	THERAPEUTIC USE
D1 AND D5 AGONISTS	1-PHENYL 2,3,4,5 TETRAHYDRO 7,8 DI-HYDROXY-1H-3 BENZAZEPINE (SKF 38393)	----------
D1 AND D5 ANTAGONISTS	3-METHYL-1 PHENYL 2,3,4,5, TETRAHYDRO 7-CHLORO 8-HYDROXY 1H-3-BENZAZEPINE (SCH 23390)	----------
D2 AGONISTS	BROMOCRIPTINE	For the treatment of Parkinson's disease and prolactin tumors
	QUINPIROLE	……
	APOMORPHINE	For inducing emesis in conditions of food poisoning
D2/ D1 AGONIST	PERGOLIDE	For preventing emesis
D2/D1 ANTAGONIST	CHLORPROMAZINE	Typical neuroleptic used for the treatment of Schizophrenia
D2 ANTAGONISTS	HALOPERIDOL SPIPERONE SULPIRIDE RISPERIDONE	Typical and atypical neuroleptics used for the treatment of Schizophrenia
D3 AGONIST	QUINPIROLE 7-HYDROXY-2-DI-N-PROPYLAMINO TETRALIN (7-OH-DPAT)	----------
D3 ANTAGONISTS	HALOPERIDOL (low affinity) RISPERIDONE (high affinity)	Typical and atypical neuroleptics used for the treatment of Schizophrenia
D4 ANTAGONIST	CLOZAPINE	Atypical neuroleptic that may precipitate agranulocytosis, effective for the treatment of 'treatment resistant Schizophrenia. Has affinity towards some serotonin receptors.