SYNTHESIS AND MODE OF ACTION OF TRICYCLIC ANTIDEPRESSANTS

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ABSTRACT
Depression is now common problem in human being. Antidepressive drugs are used to elevate the mood in depressive illness. All antidepressants affect, monoaminergic transmission in the brain mainly two types are antidepressant drugs which are tricycle Antidepressants and Monoamine oxidase inhibitors. They inhibits monoamine uptake and interact with a variety of receptors such as muscarine, histamine H1 and α-adrenergic, 5-hydroxytryptamine 1 and 2 and occasionally with dopamine D2. TCA2 and related drugs inhibit active uptake of biogenic amines. Tricyclic Antidepressants are imipramine, Amitriptyline, Doxepin, Dothepin Clomipramie and adrenaline inhibitors Desipramine, Notriptyline, amoxapine.

KEYWORDS: Depression Tricyclic Antidepressants are imipramine, Amitriptyline, amoxapine.

INTRODUCTION
Depression is now common problem in human being; it can be appeared at any time. Depressed person may be suffered from symptom characteristics. As sadness, hopelessness, Despair, inferiority, suicidal-preoccupation, Episodic-Frequency, insomnia; Somatic symptoms are constipation, weight loss and Headache; psychotic symptoms are Delusions, Hallucinations and Depersonalization. Antidepressive drugs are used to elevate the mood in depressive illness. All antidepressants affect, monoaminergic transmission in the brain mainly two types are antidepressant drugs which are tricycle Antidepressants and Monoamine oxidase inhibitors. Tricyclic Antidepressants are imipramine, Amitriptyline, Doxepin, Dothepin Clomipramie and adrenaline inhibitors Desipramine, Notriptyline, amoxapine. Tricyclic Antidepressants (TCA2 inhibit monoamine uptake and interact with variety of receptors such as muscarine, histamine H1, α-, 5-hydroxytryptamine1 and 2 and occasionally with dopamine D2.
Imparamine Hydrochloride

TriImparamine Maleate

Mianserin Hydrochloride

Dothiepin Hydrochloride

Amitriptyline Hydrochloride

Doxepin Hydrochloride
Protriptyline Hydrochloride

Synthesis

1. Chlorpromazine

\[ \text{m-Chloroaniline + } \text{α-Chloro benzoic acid} \xrightarrow{\text{CuCl}_2} \text{Heat} \xrightarrow{250^\circ C} \text{HOOC} \]

\[ \text{Cl} \quad \text{NH}_2 \quad \text{Cl} \quad \text{COOH} \quad \text{CuCl}_2 \quad \text{Cl} \quad \text{NH}_2 \quad \text{Cl} \quad \text{COOH} \quad \text{Heat} \xrightarrow{250^\circ C} \text{HOOC} \]

\[ \text{2-Chlorophenothiazine} \xrightarrow{\text{NaNH}_2 \text{ in Toluene}} \text{Cl} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{N} \quad \text{CH}_3 \]

2-Chlorophenothiazine

\[ \text{Cl} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{N} \quad \text{CH}_3 \]

Chlorpromazine

2. Prephenazine

\[ \text{1-Piperazineethol} \]

\[ \text{Cl} \quad \text{N} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{O} \quad \text{N} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH} \]

\[ \text{2-chloro-10-(3-chloroethyl)phenothiazine} \xrightarrow{\text{HCl}} \text{reflux with secamid in toluene} \]

\[ \text{Cl} \quad \text{N} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{OH} \]

Prephenazine
3. Thioridazine

2-chloro Prephenazine

- HCl

reflux with sodamide in toluene

2(Methylthio)-phenothiazine

Thioridazine
4. Amitriptyline

\[
\text{Dibenzo cyclohepta-dien-5-one} + \text{3-Dimethylaminopropyl chloride} \xrightarrow{\text{Tetrahydrofuran}} \text{ether} \xrightarrow{\text{reflux}} \text{Amitriptyline}
\]

5. Trifluoperazine

\[
\text{2-Trifluoromethylphenothiazine} + \text{3-(4-Methylpiperazine-1-yl)propyl chloride} \xrightarrow{\text{NaNH}_2} \text{Trifluoperazine}
\]
Monoamine Oxidase Inhibitors (MAO)

Phenelzine Sulphate

Tranylcypromine Sulphate

Isocarboxazid

Chlordiazepoxide Hydrochloride

Diazepam

Oxazepam
Mode of Action

Tricyclic Antidepressants (TCA₅): They inhibit monoamine uptake and interact with a variety of receptors such as muscarine, histamine H₁, α₁-adrenergic, 5-hydroxytryptamine 1 and 2 and occasionally with dopamine D₂. TCA₅ and related drugs inhibit active uptake of biogenic amines. In depressed patients little acute effects are produced by TCA₅, except sedation. After giving these drugs continuously 2 to 3 weak the mood of patients is gradually elevated and becomes more communicated and start taking interest in self and surrounding. This, TCA₅ are not euphoriants but only antidepressants, in not proper sleep these drugs are more applicable and this phase is suppressed awakening during night are reduced. The more sedative drugs are suitable for depressed patients showing anxiety and agitation. The less sedative drugs are better for withdrawn and retarded patients. The TCA₅ lower seizure threshold and convulsion in over dose. Clomipramine; maprotiline and bupropion have the highest seizure precipitating potential. Amitriptyline and imipramine depress respiration in overdose only TCA₅ and related drugs inhibit active uptake of biogenic amines. TCA₅ and related drugs inhibit active uptake of biogenic amines Noradrenaline and 5-HT (5-hydroxy Tryptamine) into their respective neurons and thus potentiate them. They differ in their selectivity and potency for different amines. Most of the compounds do not inhibit DA (Dopamine) uptake, except bupropion, Amphetamine and cocaine which are strong inhibitors of Dopamine uptake they are not antidepressants but can play important role in Central nervous system stimulation. However, it has been found that TCA₅ indirectly facilitate dopaminergic transmission in forebrain that may play role in mood elevation. Inhibition of DA uptake correlates with stimulant action but it is not involved basically in antidepressant action and inhibition of NA (Noradrenaline) and 5-HT (5-hydroxy Tryptamine).

Several findings indicate that uptake blocked is not directly responsible for antidepressants action, uptake blockade occurs quickly but antidepressant action appears after few weak now considering mianserin is one of the antidepressant but does not show blocking action. Initially the presynaptic α₂ and 5-HT₁ autoreceptors are activated by the increased amount of NA/HT in the synaptic cleft resulting in the decreased firing of locus coeruleus (noradrenergic) and raphe (serotonergic) neurons. On long term administration antidepressants desensitize presynaptic α₂, 5-HT₁ₐ, 5-HT₁₅ auto receptors and induce other adaptive changes in the number and sensitivity of pre and post synaptic NAand/or5-HT receptors as well as in amine turnover of brain, finally it is found the enhancement noradrenergic and serotonergic transmission. Thus, uptake blockade appears to initiate a series of time dependent changes that culminate in antidepressant effect. Most tricylic antidepressant is more potent anticholinergic which show adverse effect as dry mouth, blurring of vision, constipation and urinary hesitancy. They show effect on cardiovascular function and may be dangerous in over dose. They potentiate exogenous and endogenous NA by blocking uptake, having weak α₁ adrenergic blocking action for example amitriptyline, doxepin, trimipramine show slight H₁ antihistaminic action.

MAO is a mitochondrial enzyme which plays a role in oxidative deamination of biogenic amines as adrenalin, norepinephrine, dopamine and 5-hydroxy tryptamine. MAO-A deaminates norepinephrine and 5-hydroxy tryptamine and are inhibited by clorgynline and mocloblemide. MAO-B deaminates phenyl ethylamine.
and is inhibited by seligiline. Dopamine can be deaminated by both the is enzymes.

CONCLUSION
TCA's potentiate CNS depressants; including alcohol and antihistaminic which also abolish the antihypertensive action of guanethidine and clonidine by preventing their transport into adrenergic neurons. They potentiate directly actin sympathomimetic amines and inhibits the action of indirect sympathomimetics. They have good oral absorption which are metabolise in liver, the major route for imipramine and amitriptyline is demethylation whereby active metabolites-desipramine and nortriptyline respect are formed. Mechanism of action of anti-depressants drugs is based on activities of the tricyclic antidepressants agents.

It is suggested that the antidepressants drugs increase the availability of biogenic amines at their post synaptic receptor site in brain and reverse the depression. Imptrant drugs which are tricycle are imipramine, Amitriptyline, Doxepin, clomipramine and Trimipramine.

REFERENCES