INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH & DEVELOPMENT

ISSN: 2278 – 0211 (Online)

Chemopharmacological Correlation Of Antidepressant Structures For Drug-Design

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Abstract:
The chemopharmacological correlation is based on the principles of chemical pharmacology. Possibly it may be new attempt to design antidepressant of therapeutical specificity, by correlating the antidepressive structures of natural origin and synthetic through molecular association or simplification. Serotonim and Norepinepherine selected as the structural standards. They have Indolyl, catechol, aliphatic chain of two carbons and the protonated tertiary nitrogen at the physiological pH are topographical entities for the receptor affinity and intrinsic efficacy of pharmacodynamic value, thus induce the conformational change for the biological response.The structural diveregence of non-SSRIs was rationalized by agumentation, receptor diversification and topographical selectivity. Mitrazepin, Neurontin, Pregabalin and Tramadol have special structural values. Receptor specificity and critical moieties of agonist, partial agonist and antagonist studied for finding out their role in correlation. The overall chemopharmacological correlation has empirically defined the partial components of antidepressive receptor specificity as indolyl, tertiary nitrogen, catechol and aryls. The concepts of isosterism and bioisosterism were not considered. The topographical entities of antidepressants belonging to natural and synthetic, termed as critical for utilizing them for the molecular design.

1.Introduction

The chemical diversity has a wide array of the functionalities. The novel chemical entities are designed by the method of variation[1] for modifying potency, toxicity, specificity stability, duration of action and cost of production. Two Methods of variation[1] are applied.

- Molecular simplification (Dysfunction or dissection) generally, it is applied to complex and rigid chemical structures, preferably natural products
- Association (conjunction). It is of three types
  - Molecular addition: - Association of different moieties through weak forces, e.g. H-bonding, electrostatic attraction
  - Molecular replication: association of identical moieties through covalent bond formation association of two moieties called molecular duplication, of three molecular triplication so on.
  - Molecular hybridization: Association of different or mixed moieties through covalent bond formation. This methodology pertains to analog-design and modification of lead structure, using the concepts of isosterism and bioisosterism.

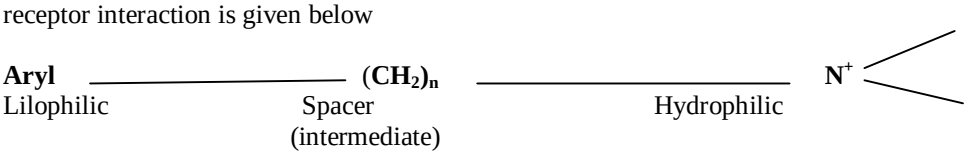
The Chemopharmacological correlation is simple theoretical approach for receptor-oriented drug action. The receptor selectivity targets specific bioaction, through critical functionalities which are involved in drug-receptor complex formation, (DRC) and essential for the response. The non-critical functionalities do not interact with receptor and suspectible to wide structural variation. The structural diversity of natural products, synthetic, nutraceuticals and serotoninergics for the chemopharmacological correlation and divergence was taken in to account.

Stereochemically, CNS receptors are chiral entities, therefore, sites of sction are more specific than vascular smooth muscle. 5-hydroxytryptamine receptor (serotonergic)[2] is widely distributed in CNS[3] and implicated in depression[4-8], anxiety and social phobia.

Seronotin selective reuptake inhibitors (SSRIs) selectively block reuptake of 5-HT at synapses and enhance the neurotransmission of happy hormone[9-12].

2.Theoretical Methodlogy

The chemopharmacological correlation strategy[13] implied that chemical structures related to receptor specificity are vunerable for the antidepressive design. Serotonium, norepinepherine were selected as the structural standards.The general structure, essential for receptor interaction is given below



The structural briefs at nuclear and peripheral levels of various chemical classes of antidepressants are given in the table-one.

Chemical classes	Nuclear functionalities	Peripheral functionalities
1. Synthetic antidepressants:	Aryl, naphthyl, anthracene Cyclopropyl, cyclohexyl Spirofusion of cyclopentyl and 2,5, pyrroldione Heterocyclics • 7 or 8 membered – Azepine, oxepine, theipin, 1-aza-2-oxo octane • 6-membered- Morpholino, piperazine, piperidine, pyridine • 5-membered- Dioxane, thiazole,triazole	alkyls (methyl, ethyl, propyl, butyl and t-butyl) halogens (chloro, fluoro, trimethylfluoro), oxygens, (methoxy, oximyl, carbonyl) and nitrogens, (methylamino, dimethylamino, amide, hydrazinyl)
2. Tricyclic antidepressant	Dibenzo-azepine, aryls	Propyl, Protonated Primary or Secondary amino group
3 Nutraceuticals	alloxazine, steroidal, bicyclic, bezopyrone Octadecatriene system of fatty acid, aryls and heterocyclic (pyrimidine, pyridine, imidazoline, thiazole, thiazole, thiophene	methyl , isopropyl, ethylenic, primary amino, amide, hydroxyl, carboxy and catecholic functions.
4 Marine natural products	indole , imidazoline, and cyclohexenyl	ethylenic unsaturation and N-methyl functions
5.Terrestrial natural products	steroidal, 1-aza-2-oxo-octane, napthodianthrone, 5,7 dihydroxypyran, pyrropipiredine and catechol	carboxy, ethylenic, epoxy, hydroxyl, isopropyl, methyl, methoxy and lactonic functionalities.

Table 1: Structural Briefs Of Antidepressants[13]

The tabulated data indicated that critical moieties of topographical significance are aryl, alkyl, protonated nitrogen, indolyl and catecholic which are matching to the structural standards. The structural divergence was rendered by hetrocylics and acyclic with agumentation of antidepressive action through intracting with receptors associated with depression. , Ketamine, Mitrazepin , Neurontin , Pregablin and Tramadol have special structural values.

The following chemical names reflected structural divergence from the standards, mostly they are non SSRIs[3]

- Amoxepine -2-chloro-11-(1-piperazinyl) dibenzo (b,f) [1,4] oxazepine.
- Fluoxetine- (+) N-methyl-3-phenyl-3(4-trifluoromethyl phenoxy) propylamine
- Fluvoxamine: (E)-5- Methoxy-1-4 trifluoromethyl phenyl-pentan-2-(aminoethyl)-oxime
- Ketamine: 2-(o-para chlorophenyl)-2-methylamino cyclohexanone
- Mitrazepine(+)-2-methyl-1,2,3,4,10,14b-hexahydro pyrazino [2,1-1] pyrido [2,3,c] [2] benazepine
- Neurontin: 1-(aminomethyl) cyclohexane acetic acid.
- O-desmethyltramadol (active metabolite of tramadol)
- Paroxetine : (3S-trans)-3-[(1,3 Benzodioxol-4-5 yloxy) methoxyl] 4-(4-fluorophenyl) piperidine
- Pregabalin 3(S)-3- (aminomethyl)-5-methyl hexanoic acid

- Setraline (cis) -4- (3,4,dichloro phenyl) -1,2,3 tetrahydro-N-methyl-1-napthal enamine.
- Tapentadol (Dimethyl amino)-methyl-1-(3-hydroxy phenyl) cyclohexanol
- Tramadol (Dimethylamino)-methyl-1-(3-methaoxyphenyl)cyclohexanol
- Venlafaxine (+) 1(Dimethylamino)-1-(4-methoxyphenyl)ethyl cyclohexanol
- Citalopram (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-carbonitrite.

3.Discussion And Result

The chemopharmacological correlation among all of them exhibited remarkable degree of pharmacophoric identity. The study of this correlation led us to derive the following inferences:

- Lipophillic alkyl, aryls, heteroaryl and long chain aliphatic unsaturation speed up CNS penetration and onset of action.
- Oxygen functions furnish the greater facet for H-bond acceptor sites
- Protonated nitrogen functions enhance ionic-bonding
- The conformational rigidity and flexibility of ring system influence pharmacological selectivity. Tricyclic system has multiple receptor interactions with rise in side effects and loss of antidepressive efficacy. Tetracyclic system (amoxepine) has better selectivity and improved efficacy. The conformational flexibility of SSRI,s with fluoro/ trifluoromethyl functions enhance 5-HT receptor affinity with improved safety and tolerability.
- Antidepressant nutraceuticals[14] act as precursors for the synthesis of meurotransmitters associated with mood elevation . They act as chemical messenger in the brain and of mood regulating neurotransmitters, especially 5-HT and NE . High glycemic carbohydrates play havoc with insulin which can result in unpleasant/depressive moods, herefore higher intake of aminoacids for biosynthesis of biogenic amine with bioenergetic role of vitamins provide nutritional therapy for the depression. Omega-3-fatty acids of trans-stereochemical orientation also synerize the antidepressive action.
- Antidepressant terrestrial natural products might undergo enzymatic/metabolic degradation to antidepressant hormones. Estrogens prevent postmenpausal depression by relieving anxiety. Testosterone provides sexual energy in women with antidepressant effect. A decline in testosterone precipitate depressive episodes which can be prevented by intake of natural products as substrates of steroidgenesis.
- Marine natural products have chemical resemblance with the antidepressant structures. Aplysinopsins[16] have indolyl, oxo, and tertiary nitrogens of pharmacophoric nature for 5-HT receptor binding. 5-HT and NE may be contributory to the antidepressant agonism. It hints the selectivity of receptors. The catecholic moiety type agonists/antagonists prefer adrenergic receptor, and indole moiety type of agonists/ antagonists would be reasonable fit for 5-HT receptor.The structural group of indole alkylamine includes tryptamine, partial ergolines nontryptamine indole etc. The have chemical dominance in agonist, partial agonist and antagonist for the receptor selectivity. The structural character of aminotetranilines, aryl piperazines, alkoxy alkylamines and aryl biguanicles offers cationic, hydrophobic and H-bonding entities of the topographical significance.

5-HT is the coordinator of all the neuronal pathways related to depression. The delayed on set of action and adverse side effects diluted the clinical value of SSRIs. The structural divergence of non-SSRIs shows molecular association and dissociation of structural moieties, for the compensation of drawbacks and enhancing effectiveness in depression causing etiologies. This can be accomplished in three ways.

- Augmentation :- Fluoxetine, Paraoxetine, sertaline and spirones are useful augmenters derived by the structural variations.
- Receptor diversification:- Mitrazepin, Neurontin, Tramadol and Pregablin have special receptor-oriented structural values, involving adrenergic, opiate and voltage –gated ion channel receptors.
- Modifications of structural functionalities for improving topographical selectivity:- The oximyl group imparts geometrical isomerism by modifying Fluoxetine. (E) – Fluvoxamine becomes potent Sigma 1 receptor agonist in the class of SSRIs Pregabalin 3(S) –3- (aminomethyl) -5- methyl hexanoic acid, is a chiral synthetic molecule. The chiral modification gives topographical selectivity to chiral receptors of CNS.

The modern medical breakthroughs linked pain to depression[19]. Both share the same neural circuitry. The neurotransmitters and hormones modulate the healthy brain, as, 5-HT and endorphins control the depression. The chronic pain uses up 5-HT in brain. It is not just a sensory or affective or cognitive state but may lead to biological disaster. Modern gene chip technology identified about sixty pain related genes, confirming the response of neurons to pain. The damaged or abnormal Na+ ion channels in sensory neurons contribute to pain. The negative hormones e.g. Cortisol are adversely effect immune system.

The structural values of few exceptional antidepressants are enumerated below:

- Ketamine[20]: is rapid relief of depressive symtoms. It appears that Ketamine repairs synaptic connetions between brain cells that have badly affected by depression.
- Mitrazepine[21,22]: has faster onset of action. Nonadrenergic and specific Serotonergic tetracyclic antidepressant. It is found to be superior to all twelve popular antidepressants including SSRIs, SNRIs, and Trazodone. The chirality and receptor diversity explain its supericrity. Racemic mixture is clinically useful. It acts as partial agonist at 5-HT_{1a} antagonist at 5-HT_2 and inverse agonist at 5-HTc, this all patially contribute to antidepressive efficacy. “Azepine” ring is sandwiched between aryl and pyridine, with structural resemblance to benzodiazepines. It may diversify bioactivities towards anti-anxiety and anti-social phobial.

- Neurontin[23,24]: Structurally related to GABA and 3rd line antidepressant for neuropathic pain without 5-HT activity. It binds to sub unit of voltage activated calcium channels in neoerotex and hippocampus with nerve and mood stabilizing effect.
- Pregabalin[25,26]: Flexible and chiral synthetic molecule, effective for both pain and mood elevation and stabilization. It has definite mood brightening effect.
- Tramadol[27-30]: instant cure for depression and helpful in stressful headaches and decent sleep. Tramadol is marketed as a racemic mixture of the (1R,2R) and (1S,2S) enantiomers with weak affinity for the u- opioid receptor. The (1R,2R)-(+)-enantiomer is HT reuptake, whereas the (1S,2S)-(-)-enantiomer is responsible for noradrenaline reuptake effect.

Tapentadol is te structural relative of Tramadol, having phenolic group. Tramadol is u-opioid receptor agonist (analgesic effect) and 5-HTc antagonist reduces depressive, obsessive-complusive symtoms in patients with pain. It is metabolized to primary active metabolite, O-desmethyltramadol, more potent u-opioid agonist than tramadol, Tramadol is partially a prodrug, O-desmethyltramadol is SNRI and $5HT_{2c}$ receptor antagonist.

- Molecular association:- The cyclohexanol and dimethyl amino moieties derived from Levorphanol and Venlafaxine whereas methoxy phenyl selected from codeine because Tramadol has structural resemblance with them. Their association designed chiral structure of Tramadol. Sterochemically recemic mixture of Tramadol and Venlafaxine are clinically useful.
- Molecular Simplification:- Tramadol is the stripped version of codeine.
- Topographical phenoleentities of receptor diversification: Tramadol and Tapentadol offer cationic nitrogen, aryl entities for the topographical complementariness of opioid, adrenergic and 5-HT receptors at anionic, hydrophobic ad H-bonding sites. Tapentadol and phenyephrine have metaphenol attached to aliphatic chain with terminal nitrogen, their interaction with alpha-adrenergic receptor therefore share clinical usefulness of Tapentadol in treatment of nasal congestion.

It is noteworthy that opiate receptor agonism and NE reuptake inhibitory action rendered a remarkable empathogenic and antidepressive effects to Tramadol at the same doses of SSRIs

4.Conclusion

An ideal antidepressant is to stabilize and mormalize the neurotransmitters-serotonin, norepinepherine, dopamine, because they regulate mood, thought, behavior and energy levels. 5-HT and NE was selected as the structural standard for the chemopharmacological correlation. The structural divergence compensated the demerits of SSRIs through agumentation, receptor diversification and topographical selectivity imparted by chirality for complement to chiral receptors of CNS. The antidepressive actions of Mitrazepin, Neurontin, Progablin, Ketamine and Tramadol were interpreted on the basis of special structural make up. Finally depression is not a weakness of mind, will or spirit but lack of hope and motivation Antidepressants are auxillary support but not the ultimate cure.

5.Acknowledgement

Dr. Luvkush (Academic advisor) express his gratefulness to Shri S.P. Singh (chairman) and Dr. G.D. Singh (Managing Secretary) for respecting the hardwork of theoretical research on the marine biomolecules and life-style drugs. The Co- author indebted to them for appreciating his efforts. Shri Kshitiz Nagrath is thankfully acknowledged for the help in preparing this manuscript.

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