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Antidepressant and Anti-Inflammatory Activities of Cationic Amphiphilic Complexes of Sulphadiazine

K.Hariprasath[1], I. Sudheer babu[2] and P.Venkatesh[3]

[1] Adarsa College of Pharmacy

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Abstract

In our study we synthesized schiff? base of sulphadiazine on treating with aromatic aldehydes like para diethyl amino benzyldehyde and paradimethyl amino benzyldehyde. The synthesized schiff?s bases were converted to its cationic amphiphilic bases by treating with methyl iodide. The cationic schiff bases were converted to metal complexes by treating with metals like copper chloride (CuCl2), zinc chloride (ZnCl2) and cadmium chloride (CdCl2). All the synthesized compounds were characterized by elemental analysis, IR and H1 NMR. Synthesized compounds were screened for anti-inflammatory and antidepressant activity. Copper metal complexes showed excellent anti-inflammatory activity and zinc metal complexes showed excellent antidepressant activity.

Index terms— cationic amphiphilic bases, schiff? base, metal complexes, anti-inflammatory and antidepressant activity.

1 Introduction

n amphiphilic substance exhibits a double affinity, which can be defined from the physico-chemical point of view as a polar-apolar duality. When a single surfactant molecule exhibit both anionic and cationic dissociations it is called amphoteric or zwitterionic. Cationic amphiphilic drugs (CADs) are widely used in chronic pharmacotherapies in spite of frequently observed side effects connected with lysosomal phospholipid (PL) storage. Cationic amphiphilic drugs (CADs) represent compounds of different therapeutic classes such as antidepressants, neuroleptics, and antiarrhythmics. In acidic cellular compartments these drugs become efficiently protonated and thus trapped in, e.g. lysosomes. As a result of pHdependent ion trapping, total lysosomal drug concentrations may exceed extracellular levels by orders of magnitude. Lysosomotropic drugs may inhibit lysosomal phospholipid (PL) metabolism leading to the formation of dense cytoplasmic granules, i.e. lysosomes filled with undegraded PLs. The formation of drug-PL complexes further enhances intracellular accumulation of drugs. We all require iron, copper and zinc for normal brain function but metal metabolism becomes dysregulated in a variety of neurodegenerative diseases. Metals accumulate in Alzheimer's dementia and Parkinson's disease and are deficient in Menkes disease. Transition metals perform a wide range of biological functions in the brain. A common feature is their ability to exist in a variety of oxidation states and participate in redox reactions; thus copper, iron, and manganese are all catalytically active metals in a class of enzymes that sequester free radicals. It is useful to look at the common and varying functions of transition metals in the brain to better understand what mechanisms are disrupted in metal dyshomeostasis and how this may lead to cell death in diseases of the CNS (Tyszka, 2014).

Metal complexes are also known as coordination compounds, which include all metal compounds. Metal complex is a structure consisting of a central atom (or) ion (metal) bonded with anions (ligands). Compounds that contain a coordination complex are called coordination compounds. The bonding characteristics of complexes and alteration in size of the metal ion are related to thermodynamic aspects. The stability constants for the complexes formed from various metal ions and one ligand have a particular sequence (Banerjee, 2009, Shi, 2007).

The parent sulpha drugs Sulphadiazine is a well known antibacterial in olden days. But owing to their narrow spectrum of activity and side effects, now a days their usage is limited. In our research we improved the biological activity by different synthetic modifications, In the first step by converting the parent sulpha drug in the form of Schiff base, there by generating a lone pair of electrons in a sp2 hybridized orbital in the structure leading to the derivation of and different biological properties. In the second step of synthesis the Schiff bases were converted in to their cationic amphiphiles, which may alter their pharmacokinetic profile like distribution and binding parameters. This step helped us to improve the spectrum activity from narrow spectrum to broad spectrum activity, increasing the permeability of drug molecule in brain to cross blood-brain barrier, which improves the antidepressant property, and release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity. In the third step by deriving metal complexes of copper and zinc the biological properties like antidepressants and anti-inflammatory activities were strongly elucidated.

2 a) Synthesis of Schiff's Base

The Schiff's base has been synthesized by refluxing the reaction mixture of hot ethanolic solution (30 ml) of Sulphadiazine (0.01 mole) with hot ethanolic solution (30 ml) of different aromatic aldehyde (0.01 mole) for about 2-3 hours at 60-70 0 C (Fig- 1). The mixture was allowed to stand over night. After that the colored solid product was filtered off, re-crystallized with ethanol and finally washed with petroleum ether. The final product was dried under reduced pressure over anhydrous calcium chloride (Panneerselvam, 2005). and refluxed for 6 hours (Fig- **??**). The reaction mixture was left overnight to complete the precipitation of the products. The products were recrystallized with ethanol to obtain pure products (Ibotomba, 2012, Ajaykumar, 2009). Animal's Swiss albino mice (20-25gm) and Male Sprague -Dawley rats (160-180) were maintained at standard diet and ad libido. The experiment protocol was approved from institutional ethical committee. The test compounds were dissolved in 3 % DMSO administered orally to different groups with increasing doses. Six animals were taken in each group. Mortality was determined after 24 hours of treatment. The dose, at which the 50 % mice survived, was considered as LD50 value of the compound (OECD, 2002).NH 2 S O O C H N N S O O O C H N Ethanol 60-70oC 3 hrs R R 1 R R 1 H N N N NH N N Compound A R-C 2 H 5 , R 1 -C 2 H 5 Compound B R-CH 3 , R 1 -CH 3N S O O C H N R R 1 CH 3 + I- N S O O C H N R R 1 CH 3 + MCl2 Reflux in ethanol MI2Cl2 2 2-H N N N NH N N Compound A R-C 2 H 5 , R 1 -C 2 H 5 Compound B R-CH 3 , R 1 -CH 3 MCl 2 -CuCl 2 ,

3 e) Anti depressant activity

Male Sprague -Dawley rats weighing 160-180 grams were divided into eight groups of six animals each. The test groups received orally 20 mg/kg of each sample. The reference group received imipramine (5 mg/kg, p.o) while the control group received vehicle (1 % CMC). Naïve rats are individually forced to swim inside a vertical Plexiglas cylinder (height : 40 cm ; diameter : 18 cm ; containing 15 cm of water maintained at 25 oC). Floating behaviour during this 5 minutes period has been determined in different groups of rats. The percentage inhibition was calculated by the formula **??**Kulkarni, 2010).

4 Percentage inhibition =

Before treatment -After treatment X 100 Before treatment f) Anti inflammatory activity Swiss albino mice were divided into eight groups of six animals each. The test groups received orally 20 mg/kg of each sample. The reference group received diclofenac sodium (10 mg/kg, p.o) while the control group received vehicle (1 % CMC). All the animals should make a mark on both hind paws just beyond tibiofasial junction, so that every time the paw is dipped in mercury column up to fixed mark to ensure constant paw volume. After drug administration inject 0.1ml white egg portion to the plantar region of left paw of control as well as treated group. The right paw serve as reference non inflamed paw for comparison. The inflammation was quantitated in terms of ml i.e. replacement of water by edema using a Plethysmometer immediately before egg white injection and then 0, 1, 2 and 3 hours after egg white injection. The percent inhibition of edema as calculated for each group with respect to its vehicle treated control group. The antiinflammatory activity was calculated by using the relation used by % inhibition = (Vc-Vt/Vc) x 100 Whereas Vc was the average inflammation (hind paw edema) of the control group of mice at a given time, Vt was the average inflammation of the drug treated (i,e sample or reference diclofenac sodium) mice at the same time (Sathe, 2011).

5 g) Statistical analysis

The data were expressed as mean ±SEM.

Statistical analysis was performed one-way ANOVA followed by Dunnett"s multiple comparison test using sigma stat software (version 2.0, Jandel Scientific Inc. USA a) Characterization of synthesized compounds A1-Copper metal complex of (E)-N- **??**

6 Results and Discussion

b) Anti inflammatory activity of synthesized compounds Anti inflammatory activity was carried by paw oedema method using diclofenac sodium as standard. The results are given in the table-1. Currently used

antiinflammatory drugs are associated with some severe side effects. Therefore, the development of potent antiinflammatory drugs with fewer side effects is necessary. A major factor limiting their use is gastrointestinal toxicity. In recent years, Schiff bases are widely used in formulating various types of drugs for their diversive biological activities. Metal complexes of Schiff bases have also been used as anti-inflammatory and antiarthritic agents. Anti-inflammatory of Zn (II) and Cu(II) complexes of indomethacin has been reported previously (Venugopala, 2003, Wei, 2006, Alam, 2012& Sondhi, 2006), based on this we have evaluated antiinflammatory activity of synthesized metal complexes.

The down regulation of pro-inflammatory mediators through interaction of cationic lipids with the PKC pathway may explain this anti-inflammatory activity. Furthermore, since cationic lipids have intrinsic antiinflammatory activity. Studies indicating that the release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity (Mario, 1997). Results revealed that the copper metal complexes (20mg/kg.b.wt) of Schiff bases of sulpha drugs A1, B1 showed excellent anti-inflammatory activity in carrageenan induced edema method by comparing with standard drug diclofenac sodium (10mg/kg.b.wt). It was thus confirmed that copper complexes, a unique class of potentially more therapeutically useful antiinflammatory drugs. These results demonstrate that cationic lipids can be considered as novel antiinflammatory agents.

Table1 : Results of in vivo anti inflammatory activity of metal complexes of schiff's base of Sulphadiazine The most probable causes for depression are connected with the loss of homeostasis of the stress hormones, neurotransmitters, and disturbed trace elements levels. It has been reported that successful depression therapy can lead to zinc level normalization. It is reported that early life stress is a major risk factor for development of later depression due to affected neurogenesis in brain, especially in hippocampus. On the molecular level, these processes may be zincdependent via antioxidative activity changes and its influence on proper course of brain development process (Malgorzata, 2014, Chandramouli, 2012). There is an evidence for the role of mitochondrial dysfunction in the pathophysiology and treatment of neurodegenerative diseases, including mood disorders (Kato, 2000, Stork, 2005). Respiratory rate is a parameter characterizing functioning of the oxidative phosphorylation. The mitochondrial hypothesis states that impaired energy metabolism of brain cells is involved in the pathophysiology of antidepressants. The therapeutic or side effects of drugs administered in the treatment of depression may involve the targeted regulation of mitochondrial functions. In previous study it is reported that there is a direct mitochondrial targeting is involved in mechanisms of action of pharmacologically different antidepressants. Antidepressants are potent partial inhibitors of mitochondrial respiration (Jana, 2012).

7 IV.

8 Conclusion

Cationic amphiphilic drugs (CADs) represent compounds of different therapeutic classes such as antidepressants, neuroleptics, and antiarrhythmics. In their neutral, lipophilic form cationic amphiphilic drug enter cells and their organelles. In acidic cellular compartments these drugs become efficiently protonated and thus trapped in, e.g. lysosomes. By increasing the permeability of drug molecule in brain to cross blood-brain barrier, which improves the antidepressant property and release of cationic lipids into the macrophage cytoplasm is a necessary step for anti-inflammatory activity.

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Figure 1: Figure 1 :

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Figure 2:

Figure 3:

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Group		Dose	0 hour	Paw volume (ml) 1 hour	2 hour
Control Group-II		1% CMC (20mg/kg b.wt)	0.2 0.2 0.2 0.2 0.2 0.3 0.3 0.3		
			0.3	0.4	0.2
			0.3	0.4	0.2
			0.2	0.3	0.2
			0.3	0.5	0.4
	Compound		0.3	0.6	0.4
Group-III	1A2	(20mg/kg b.wt)	0.3 0.2 0.3	0.5 0.4 0.4	0.4 0.2 0.3
			0.3	0.5	0.4
Group-IV	Compound	(20mg/kg	0.3	0.5	0.5
	1A3	b.wt)	0.3	0.6	0.4
			0.2	0.4	0.3
			0.3	0.5	0.4
			0.3	0.6	0.5
			0.3	0.5	0.5
Group V	Compound	(20mg/kg	0.3	0.4	0.2
	1B1	b.wt)	0.3	0.3	0.2
			0.3	0.3	0.2
			0.3	0.4	0.1
			0.3	0.4	0.2
			0.3	0.3	0.2

Figure 4: Table 2 :

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