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Protective Roleof Sigma Receptor Ligands Against Myocardial Infarctions

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Abstract
Cardiovascular diseases (CVDs) are major reason of mortality and morbidity worldwideMyocardial infarction is a cardiovascular disease occurs due to blockage in the coronary artery by atherosclerotic clot. Coronary artery blockage interrupts the coronary blood supply which destroying cardiac tissue. Multiple factors such as inflammation, β-adrenergic system as well as oxidative stress are involved in the causing the myocardial infarction. Certain sigma receptor agonist show protective action against myocardial infarction.The main purpose of this article is to understand thepotential of sigma receptor agonist forcardiovascular protection .Sigma receptor stimulation represents a new therapeutic strategy for the treatment of heart from hypertrophic as well as dysfunction in heart failure.Sigma receptor primarily potentiating the cholinergic neurotransmission and modulate the cardiac contractility.

1. SIGMA RECEPTOR

The sigma receptors are escort proteins hypothesized by martin and cowerkers in 1976 dependent on activity of SKF10,047 (N-allylnormetazocine) and related benzomorphans. The name sigma is taken from essential letter "s" in SKF 10,047, which tie to various receptor protein .In spite of the fact that these receptors were earlier discovered as a subtype of one of the narcotic types receptors (σ narcotic receptor), yet presently affirmed to be a non-narcotic receptor that dilemma different psychotropic medications (1,2).

Sigma receptors are in a general sense arranged in the cerebrum and different organs that fill in as centers for psychostimulant drugs, including the heart and lung. Sigma receptors are on a very basic level groupings into two receptors that is sigma 1 receptors and sigma 2 receptors. Sigma 1 receptor fundamentally helping in redesigning cholinergic neurotransmission through the neirones. (3) A couple of sigma 1 receptors agonists, for instance, berberine,, Sertraline, Fluxetine and fluvoxamine, etc show protective effect for myocardial dead tissue. In rat hearts, sigma agonists for the most part modify the cardiovascular contractility (4). In heart muscles, choking influences produced by sigma receptor ligands was first reported in rat neonatal refined cardiomyocytes . A short time later, sigma receptors were moreover found in the plasma layers of adult rat ventricular heart tissues (5). Furthermore data on the effects of sigma ligands in rat withdrew hearts have been represented (6, 7, 3) and repeated treatment with sigma ligands cause desensitization of sigma receptors in heart muscle (8).
Pharmacological and biochemical investigations have grouped the sigma receptors into two type sigma-1 and sigma-2 receptor. These two receptors separate dependent on the one of a kind remedy selectivity layout and sub-atomic mass. The extraordinary sub-atomic weight turned into discovered between sigma receptor subtypes, the sigma-1 receptor is 29-KDa single polypeptide, whearas sigma-2 receptor have sub-atomic load of 18.21-KDa. The sigma-1 receptor is restricted inside the endoplasmic reticulum(ER) of the mobile and

translocate inner cells whilst empowered by means of ligands to oversee molecule channels and neural connection launch (10)Dextrorotatory isomers of sigma ligand show selectivity for sigma-1 restricting site while levorotatory isomer show liking for sigma-2 restricting site (11).

2. CARDIOPROTECTIVE EFFECT OF SIGMA LIGAND

Variety of compounds are bind to sigma receptors such as benzomorphones, morphinons, phenothiazines etc. many of them are psychotropic drugs and are in clinical practice for the treatment of psychoses(**12,13**).
Sigma ligands shows effect against myocardial infarction

Berberine, is belonging to isoquinoline alkaloid and is obtained from herb *Coptis chinensis* (Huanglian), exhibit wide variety of activities likes antihypertensive, antimicrobial, antidiarrhoeal, antidiabetic, antiproliferative and anti-inflammatory effect. In addition berberine reported to have the beneficial effect for the cardiovascular disease in both clinical data and preclinical data. Berberine was evaluated for its preventive effect against isoproterenol induced myocardial infarction. Berberine exert cardioprotective effect by its antioxidative and anti-inflammatory properties(**14-16).**

Fluvoxamine is high partiality sigma1 receptor agonist. It is an upper medication because of its specific serotonin reuptake inhibitor activity. Specific serotonin inhibitor (SSR!s) are known to diminish post-myocardial dead tissue and mortality (17,18). Fluvoxamine show valuable consequences for ischemia reperfusion injury in guinea pig heart by restraining opening of the MPTP, by forestalling calciumover-burden instigated apoptic cell death identified with endogenous collection of 5-HT**(19,20).**

Ketamine, 2-(o-chlorophenyl)-2-(methylamine) cyclohexanone, was introduced into clinical anaesthesia by Corssen and Domino in 1966 is a phencyclidine (PCP) and cyclohexamine derivativeIt is an intravenous sedative specialist producing a one of a kind dissociative sedative state portrayed by separation between the thalamocortical and limbic frameworks. Ketamine is considered to be the antagonist for NMDA receptors engaged with tangible contribution at the spinal, thalamic, limbic, and cortical levels. Ketamine impairs limbic functions and blocks sensory input and reuptake of catecholamines. It animates sigma receptors, alpha-and beta-adrenergic receptors and offends muscarinic receptors of the focal sensory system. Clinical information shows ketamine applies useful stimulatory consequences for cardiovascular framework. Study shows the estimations of heartbeat rate (PR), systolic pulse (SBP) and mean blood vessel pressure (Guide) were essentially raised over the benchmark (21).Moreover ketamine has anti-inflammatory property due to which it show protective action on IRI. One of the clinical study also investigated that ketamine prevent the guinea pig heart from reperfusion injury(22,23).
Anxiolytic medication afobazole has indicated agonist ligand features for sigma- 1 receptor (σ1 receptor) as well as for the MT 3 receptors. Preclinical investigations show that afobazole have cytoprotective impact through communication with both sigma-1 receptor and MT 3 receptor(24). Afobasol additionally fundamentally raised the heart fibrillation limit in creatures with flawless myocardium and took after class 1B hostile to arrhythmic medication lidocaine as far as this movement. It is expected that afobasol forestalls cardiovascular fibrillation by going about as an agonist of cytosolic sigma-1 receptors in cardiomyocytes. Against ischemic impact of afobazole in exploratory myocardial dead tissue was likewise assessed because of its association with sigma 1 receptor(25-27).

Imipramine is a tricyclic antidepressant (TCA), which have the potential to treat major depression. It also show significant effect for treating the anxiety attacks and panic disorders. The effect of imipramine was investigated using the isolated dog preparation. Studies show that imipramine lead to decrease in hypertension due to peripheral vasodilation effecr on blood vessels and also induce reduction in the baroreceptor reflexes. (28-32).

Cardiovascular system disorders belong to the most common causes of morbidity and mortality in the developed countries with an enormous impact on the population and economics. Stimulation of sigma receptor with ligand binding in the cardioprotection activity is the novel concept yet to be discovered. However various animal model studies have proved the cardioprotective activity of sigma receptor ligands such as Fisetin, ANAVEX2-73, Ketamine and PRE-034. Selective serotonin reuptake inhibitors target the sigma receptors to produce cardioprotective effects Therefore, it can be concluded that sigma receptor ligands could be useful as novel therapeutic agents.

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