REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Acute Coronary Syndrome: Beyond Conventional Treatment

Mohamed Ibrahim Ahmed[a*], Heba Mohamed Ahmed Ali[b], Yasser Mohamed Ahmed Mostafa[c,d], Dina Mohamed Khodeer[d]

[a] Department of Clinical Pharmacy, Ismailia Medical Complex, General Authority of Health Care, Ismailia 41542, Egypt; [b]Department of Physiology, Faculty of Veterinary Medicine, Suez Canal University, Ismailia 41522, Egypt; [c]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Badr University in Cairo, Cairo 11829, Egypt; [d]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt

Received: 21. 05. 2023

Revised: 13. 06. 2023

Accepted: 16. 06. 2023

***Correspondence Author:**

Tel: +201284393943

E-mail address:

mohamedibra823@gmail.com

Abstract

Acute coronary syndrome, which is the acute manifestation of ischemic heart disease, remains a major cause of morbidity and mortality across the world and is mainly responsible for 1.8 million deaths per year. The pathophysiology of acute coronary syndrome is usually due to atherosclerotic plaque rupture which results in a sequence of inflammatory events, thrombus formation, and platelet aggregation causing an aggravation of insufficient perfusion to meet myocardial oxygen demand which can eventually lead to myocardial infarction. Serotonin a monoamine neurotransmitter and a hormone found in both the central nervous system and the peripheral nervous system is released during myocardial ischemia, acute inflammation, and tissue damage leading to platelets aggregation, thrombus formation, contraction of smooth muscle cells, and coronary artery spasms. Serotonin also plays an important role in the progression of myocardial cellular injury through various pathways. This review discusses the potential therapeutic role of targeting the serotonin system in the setting of acute coronary syndrome.

Keywords: Ischemic heart disease; Acute coronary syndrome; Myocardial infarction; Serotonin.

1. Introduction

Acute coronary syndrome (ACS) is a group of conditions that are associated with acute myocardial ischemia or infarction as a result of imbalance between coronary blood supply and myocardial demand which is commonly caused by a sudden decrease in coronary blood flow due to an acute thrombus **(Smit et al., 2020)**.

2. Pathophysiology

Myocardial ischemia caused by insufficient perfusion to meet myocardial oxygen demand is the underlying pathophysiology of ACS. Inadequate perfusion is typically caused by coronary arterial vessel stenosis as a result of atherosclerotic coronary artery disease (CAD) development **(Figure 1) (Smit et al., 2020)**. CAD is characterized by thickening and obstruction of the coronary arterial vessel lumen by atherosclerotic plaques. Fibrous plaques are considered stable but can cause anginal symptoms with exercise and increased myocardial oxygen demand because of the decrease in coronary arterial blood flow through the fixed stenotic lesions. Unstable plaques are more likely to rupture, resulting in a sequence

of inflammatory events, thrombus formation, and platelet aggregation that can cause acute obstruction of the coronary arterial lumen and myocardial infarction; this rupture initiates the pathophysiological process of ACS **(Rosen's Emergency Medicine, 2018)**.

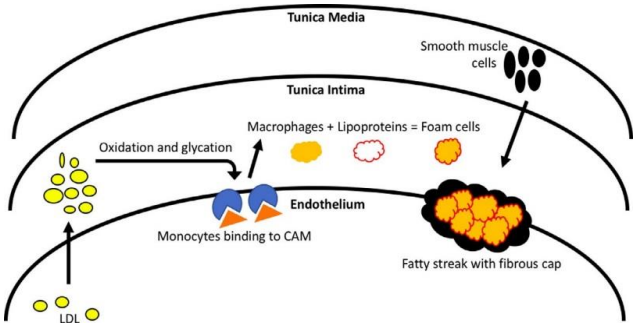

Figure 1. Initiation of coronary arteries atherosclerotic plaque.

3. Classifications

Acute coronary syndrome is divided into ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA) **(Figure 2) (Rossington, 2016; Chezar-Azerrad et al., 2021)**.

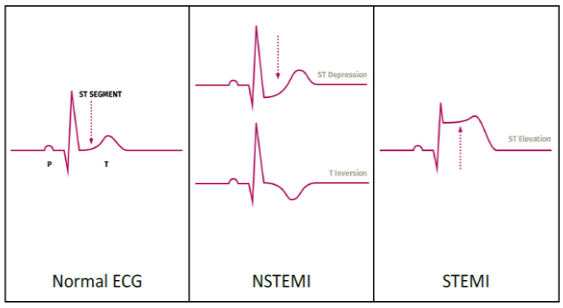

Figure 2. Electrocardiographic changes in acute coronary syndrome

The STEMI is defined by characteristic symptoms of myocardial ischemia in conjunction with persistent ST-segment elevation on electrocardiogram (ECG) with positive cardiac troponin I (TnI) representing a total occlusion of the coronary artery. In NSTEMI, despite a positive TnI, there is no ST-segment elevation which represents a partial occlusion of the coronary artery. Unstable angina is the clinical form of ACS in the absence of both ST-segment elevation on ECG and high TnI level **(Figure 3) (Pollack & Riese, 2019; Ferri, 2022)**.

4. Treatment

Initial care for ACS includes administration of morphine, supplemental oxygen, nitrates, aspirin, a

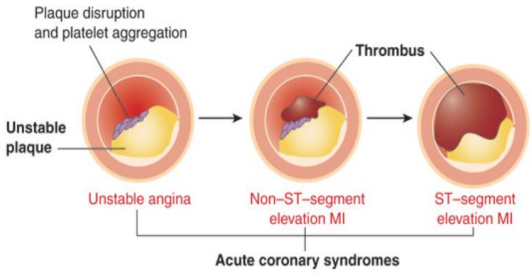

Figure 3. Pathophysiological spectrum of acute coronary syndrome.

β-blocker, an angiotensin converting enzyme inhibitor, and a statin. Antithrombotic therapy, which consists of long-term antiplatelet therapy and short-term anticoagulation therapy, is the cornerstone of ACS treatment. Therapeutic reperfusion is the treatment of choice in most patients with STEMI. Preferred option for reperfusion is percutaneous coronary intervention; alternative treatments include coronary artery bypass graft or fibrinolytic therapy **(Ibanez et al., 2018; Collet et al., 2021)**.

Patients with UA/NSTEMI may be treated using an early invasive strategy or an ischemia-guided strategy. Early invasive strategy (angiography and percutaneous coronary intervention) is recommended for patients with risk factors suggesting a high likelihood of further cardiac events. Ischemia-guided strategy is recommended for low risk patients and may also be more suitable for patients in whom other clinical conditions (severe comorbidities) or personal considerations apply. Comorbidities that can affect treatment include heart failure, chronic kidney disease, and diabetes **(Ibanez et al., 2018; Collet et al., 2021)**.

5. Role of serotonin in myocardial ischemia and infarction

Serotonin (5-HT) is a monoamine neurotransmitter/hormone found in both the central nervous system and the peripheral nervous system. 5-HT is formed from the dietary amino acid tryptophan, which is converted to 5-hydroxytryptophan in chromaffin cells and neurons by the action of tryptophan hydroxylase, an enzyme limited to 5-HT-producing cells (however not present in platelets). The 5-hydroxytryptophan is then decarboxylated to 5-HT via a non-specific decarboxylase. 5-HT is transported into cells through uptake transporters of 5-HT. Degradation

occurs primarily by monoamine oxidase, forming 5-hydroxyindoleacetic acid, which is excreted in urine **(Waller & Sampson, 2018)**.

Serotonin receptors are divided into seven classes based of their structural and functional characteristics (5-HT1 to 5-HT7) **(Waller & Sampson, 2018)**. 5-HT2 receptors are of significant clinical interest due to their involvement in the physiological and pathophysiological processes in the cardiovascular system. 5-HT2A receptors besides being found in many parts of the central nervous system **(Ritter et al., 2020)**, they are observed on the cell membranes of platelets **(Clemetson & Clemetson, 2019)**, smooth muscle cells **(Vanhoutte, 2020)**, and on cardiomyocytes along with 5-HT2B receptors **(Ayme-Dietrich et al., 2017; Monassier & Maroteaux, 2019)**.

In the cardiac tissues, 5-HT has been identified in platelets of the vascular beds, mast cells, and sympathetic nerve endings **(Shimizu et al., 2002)**; 5-HT is released from these compartments during myocardial ischemia, acute inflammation, and tissue damage **(Horibe et al., 2004; Mauler et al., 2019)**.

Binding of 5-HT to platelets 5-HT2A receptors induce more 5-HT to be released from the platelet's dense granules through a vicious cycle leading to platelets aggregation, thrombus formation, contraction of smooth muscle cells, and coronary artery spasms **(Shimizu et al., 2002; Nagatomo et al., 2004; Bampalis, 2016)**.

Serotonin accumulates in the myocardial interstitium and plays an important role in the progression of myocardial cellular injury through various pathways utilizing 5-HT2A and 5-HT2B receptors along with uptake transporters of 5-HT **(Shimizu et al., 2002; Sonobe et al., 2013; Du et al., 2017; Ayme-Dietrich et al., 2017)**.

In recent study, flibanserin demonstrate a novel cardioprotective effect against isoproterenol induced myocardial infarction in female rats **(Ahmed et al., 2023)**.

6. Flibanserin

Flibanserin (FLP) is a non-hormonal drug which is chemically described as N-alkylpiperazine derivative. FLP was first introduced as an antidepressant drug **(Invernizzi et al., 2003)**, however, in August 2015, FLP became the first drug to be approved by the Food and Drug Administration for the treatment of acquired, generalized hypoactive sexual desire disorder in premenopausal women **(Saadat et al., 2017)**.

6.1. Pharmacodynamics and mechanism of action

Flibanserin has a high affinity for 5-HT post-synaptic 5-Hydroxytryptamine 1A (5-HT1A) and 5-Hydroxytryptamine 2A (5-HT2A) receptors, displaying agonist activity on 5-HT1A receptors and antagonist activity on 5-HT2A receptors. FLP may also act as a moderate antagonist at 5-Hydroxytryptamine 2B and 5-Hydroxytryptamine 2C receptors and a partial agonist at dopamine 4 receptors **(Stahl, 2015)**.

Preferential FLP activation of 5-HT1A receptors and blockade of 5-HT2A receptors on the cortical pyramidal neurons results in the decrease of glutamate transmission to the brainstem which leads to:

a) disinhibition of the ascending adrenergic and dopaminergic neurons.

b) inhibition of the ascending serotoninergic neurons **(Stahl, 2015)**.

Together, these actions serve to increase norepinephrine and dopamine, and transiently decrease 5-HT, restoring an appropriate balance of excitatory and inhibitory activity of the brain reward centers to the prefrontal cortex. Further, it is important to highlight that FLP does not directly increase dopamine release in the reward centers of the nucleus accumbens, significantly decreasing the possibility of abuse potential **(Clayton et al., 2020)**.

6.2. Pharmacokinetics

Flibanserin is available as a 100 mg tablet which is taken orally once daily at bedtime. Maximum plasma concentrations occur 45 to 60 minutes after oral administration with a half-life of nearly 11 hours. Flibanserin reaches steady state after 3 days of oral dosing with a 33% absolute oral bioavailability, and a high (98%) affinity for proteins (predominantly albumin). Administering FLP with food, especially high-fat, high-caloric meals increase the extent of absorption, however, slows the absorption rate **(Deeks, 2015)**.

Flibanserin is extensively metabolized primarily via Cytochrome P450 3A4 (CYP3A4), with

Cytochrome P450 2C19 contributing to a lesser extent. At least 35 FLP metabolites are produced, the majority of which are present in plasma at low concentrations; only two metabolites achieve a plasma concentration similar to that of the parent drug, although neither are pharmacologically active. FLP is eliminated via feces (51%) and urine (44%) following a single oral dose of 50 mg FLP solution **(Deeks, 2015)**.

6.3. Adverse events and drug interactions

Flibanserin may result in central nervous system (CNS) depression with drowsiness and sedation. Dry mouth, fatigue, and insomnia can also occur. Patients should avoid driving or engaging in other activities that require full alertness until at least 6 hours after taking FLP. This risk can increase with concurrent use of CNS depressants such as benzodiazepines, opioids, hypnotics, and diphenhydramine. FLP can cause hypotension and syncope by itself **(Baid & Agarwal, 2018)**.

Flibanserin is contraindicated for use in combination with strong or moderate CYP3A4 inhibitors (e.g. fluconazole, ketoconazole, itraconazole), as the resultant increase in FLP concentrations can increase the risk of hypotension and syncope. FLP should be discontinued ≥ 2 days prior to initiating such CYP3A4 inhibitors and be reinitiated 2 weeks after CYP3A4 inhibitors discontinuation. CYP3A4 inducers (e.g. phenobarbital, phenytoin, rifampicin, carbamazepine) may reduce FLP exposure; coadministration is not recommended **(Deeks, 2015)**.

Taking FLP in combination with alcohol does not significantly alter the pharmacokinetic profile of FLP, although it does increase the risk of CNS depression, syncope and hypotension; therefore, alcohol is contraindicated **(Deeks, 2015)**.

7. Conclusion

Serotonin plays an important role in the progression of myocardial cellular injury during myocardial ischemia and may represent potential therapeutic target in the management of acute coronary syndrome.

References

Ahmed, M. I., Abdelrazek, H. M. A., Moustafa, Y. M., Alshawwa, S. Z., Mobasher, M. A., Abdel-Wahab, B. A., Abdelgawad, F. E., & Khodeer, D. M. (2023). Cardioprotective Effect of Flibanserin against Isoproterenol-Induced Myocardial Infarction in Female Rats: Role of Cardiac 5-HT2A Receptor Gene/5-HT/Ca2+ Pathway. Pharmaceuticals, 16(4), 502. https://doi.org/10.3390/ph16040502

Ayme-Dietrich, E., Aubertin-Kirch, G., Maroteaux, L., & Monassier, L. (2017). Cardiovascular remodeling and the peripheral serotonergic system. Archives of Cardiovascular Diseases, 110(1), 51–59. https://doi.org/10.1016/j.acvd.2016.08.002

Baid, R., & Agarwal, R. (2018). Flibanserin: A controversial drug for female hypoactive sexual desire disorder. Industrial Psychiatry Journal, 27(1), 154. https://doi.org/10.4103/ipj.ipj_20_16

Bampalis, V. (2016). Role of the serotonin transporter and the 5-HT2A and 5-HT4 receptors for platelet function in blood [Text.PhDThesis, Ludwig-Maximilians-Universität München]. https://edoc.ub.uni-muenchen.de/19094/

Chezar-Azerrad, C., Garcia-Garcia, H. M., Dan, K., Barriola, R., Kuku, K. O., Beyene, S. S., Melaku, G. D., Shlofmitz, E., Yerasi, C., Case, B. C., Forrestal, B. J., Ben-Dor, I., Medranda, G. A., Hashim, H., Maria, G. L. D., Campos, C. M., Bourantas, C., & Waksman, R. (2021). Optical Coherence Tomography based treatment approach for patients with Acute Coronary Syndrome. Expert Review of Cardiovascular Therapy, 19(2):141-149. https://www.tandfonline.com/doi/abs/10.1080/14779072.2021.1857732

Clayton, A. H., Brown, L., & Kim, N. N. (2020). Evaluation of safety for flibanserin. Expert Opinion on Drug Safety, 19(1), 1–8. https://doi.org/10.1080/14740338.2020.1707804

Clemetson, K. J., & Clemetson, J. M. (2019). Platelet Receptors. In Platelets (pp. 169–192). Elsevier. https://doi.org/10.1016/B978-0-12-813456-6.00009-6

Collet, J.-P., Thiele, H., Barbato, E., Barthélémy, O., Bauersachs, J., Bhatt, D. L., Dendale, P., Dorobantu, M., Edvardsen, T., Folliguet, T., Gale, C. P., Gilard, M., Jobs, A., Jüni, P., Lambrinou, E., Lewis, B. S., Mehilli, J., Meliga, E., Merkely, B., Mueller, C., Roffi, M., Rutten, F. H., Sibbing, D., Siontis, G. C. M., ESC Scientific Document Group. (2021). 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal, 42(14), 1289–1367.

https://doi.org/10.1093/eurheartj/ehaa575

Deeks, E. D. (2015). Flibanserin: First Global Approval. Drugs, 75(15), 1815–1822. https://doi.org/10.1007/s40265-015-0474-y

Du, C.-K., Zhan, D.-Y., Akiyama, T., Inagaki, T., Shishido, T., Shirai, M., & Pearson, J. T. (2017). Myocardial interstitial levels of serotonin and its major metabolite 5-hydroxyindole acetic acid during ischemia-reperfusion. American Journal of Physiology-Heart and Circulatory Physiology, 312(1), H60–H67. https://doi.org/10.1152/ajpheart.00471.2016

Ferri, F. F. (2022). Ferri's clinical advisor 2022, 1030-1040.e1. https://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20190006401

Horibe, E., Nishigaki, K., Minatoguchi, S., & Fujiwara, H. (2004). Sarpogrelate, a 5-HT2 Receptor Blocker, may Have a Preconditioning-Like Effect in Patients with Coronary Artery Disease. Circulation Journal, 68(1), 68–72. https://doi.org/10.1253/circj.68.68

Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., Caforio, A. L. P., Crea, F., Goudevenos, J. A., Halvorsen, S., Hindricks, G., Kastrati, A., Lenzen, M. J., Prescott, E., Roffi, M., Valgimigli, M., Varenhorst, C., Vranckx, P., Widimský, P., & ESC Scientific Document Group. (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal, 39(2), 119–177. https://doi.org/10.1093/eurheartj/ehx393

Invernizzi, R. W., Sacchetti, G., Parini, S., Acconcia, S., & Samanin, R. (2003). Flibanserin, a potential antidepressant drug, lowers 5-HT and raises dopamine and noradrenaline in the rat prefrontal cortex dialysate: Role of 5-HT1A receptors. British Journal of Pharmacology, 139(7), 1281–1288. https://doi.org/10.1038/sj.bjp.0705341

Mauler, M., Herr, N., Schoenichen, C., Witsch, T., Marchini, T., Härdtner, C., Koentges, C., Kienle, K., Ollivier, V., Schell, M., Dorner, L., Wippel, C., Stallmann, D., Normann, C., Bugger, H., Walther, P., Wolf, D., Ahrens, I., Lämmermann, T., Ho-Tin-Noé, B., Ley, K., Bode, C., Hilgendorf, I., Duerschmied, D. (2019). Platelet Serotonin Aggravates Myocardial Ischemia/Reperfusion Injury via Neutrophil Degranulation. Circulation, 139(7), 918–931. https://doi.org/10.1161/CIRCULATIONAHA.118.033942

Monassier, L., & Maroteaux, L. (2019). Serotonin and Cardiovascular Diseases. In Serotonin (pp. 203–238). Elsevier. https://doi.org/10.1016/B978-0-12-800050-2.00012-7

Nagatomo, T., Rashid, M., Abul Muntasir, H., & Komiyama, T. (2004). Functions of 5-HT2A receptor and its antagonists in the cardiovascular system. Pharmacology & Therapeutics, 104(1), 59–81. https://doi.org/10.1016/j.pharmthera.2004.08.005

Pollack Jr., C. V., & Riese, V. G. (2019). Acute Coronary Syndrome: Unstable Angina. Differential Diagnosis of Cardiopulmonary Disease, 73–96. https://doi.org/10.1007/978-3-319-63895-9_4

Ritter, J. M., Flower, R. J., Henderson, G., Loke, Y. K., MacEwan, D. J., & Rang, H. P. (2020). Rang and Dale's Pharmacology. Elsevier. https://elsevierelibrary.co.uk/product/rang-dales-pharmacology-ebook

Rosen's emergency medicine (9. edition). (2018). Elsevier.

Rossington, J. A. (2016). Acute coronary syndromes, platelets and the endothelium. 368.

Saadat, S., Panahi, Y., Hosseinialhashemi, M., Kabir, A., Rahmani, K., & Sahebkar, A. (2017). Systematic Review and Meta-analysis of Flibanserin's Effects and Adverse Events in Women with Hypoactive Sexual Desire Disorder. Current Drug Metabolism, 18(1), 78–85. https://doi.org/10.2174/1389200217666161026090333

Shimizu, Y., Minatoguchi, S., Hashimoto, K., Uno, Y., Arai, M., Wang, N., Chen, X., Lu, C., Takemura, G., Shimomura, M., Fujiwara, T., & Fujiwara, H. (2002). The role of serotonin in ischemic cellular damage and the infarct size-reducing effect of sarpogrelate, a 5-hydroxytryptamine-2 receptor blocker, in rabbit hearts. Journal of the American College of Cardiology, 40(7), 1347–1355. https://doi.org/10.1016/S0735-1097(02)02158-7

Smit, M., Coetzee, A. R., & Lochner, A. (2020). The Pathophysiology of Myocardial Ischemia and Perioperative Myocardial Infarction. Journal of Cardiothoracic and Vascular Anesthesia, 34(9),

2501–2512. https://doi.org/10.1053/j.jvca.2019.10.005

Sonobe, T., Akiyama, T., Du, C.-K., Zhan, D.-Y., & Shirai, M. (2013). Contribution of serotonin uptake and degradation to myocardial interstitial serotonin levels during ischaemia-reperfusion in rabbits. Acta Physiologica (Oxford, England), 207(2), 260–268. https://doi.org/10.1111/j.1748-1716.2012.02461.x

Stahl, S. M. (2015). Mechanism of action of flibanserin, a multifunctional serotonin agonist and antagonist (MSAA), in hypoactive sexual desire disorder. CNS Spectrums, 20(1), 1–6. https://doi.org/10.1017/S1092852914000832

Vanhoutte, P. M. (2020). Serotonin: A forgotten signal from the blood. In Handbook of Behavioral Neuroscience (Vol. 31, pp. 393–409). Elsevier. https://doi.org/10.1016/B978-0-444-64125-0.00022-0

Waller, D., & Sampson, A. P. (2018). Medical pharmacology & therapeutics. https://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20150059469