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Frontiers in Cardiovascular Drug Discovery

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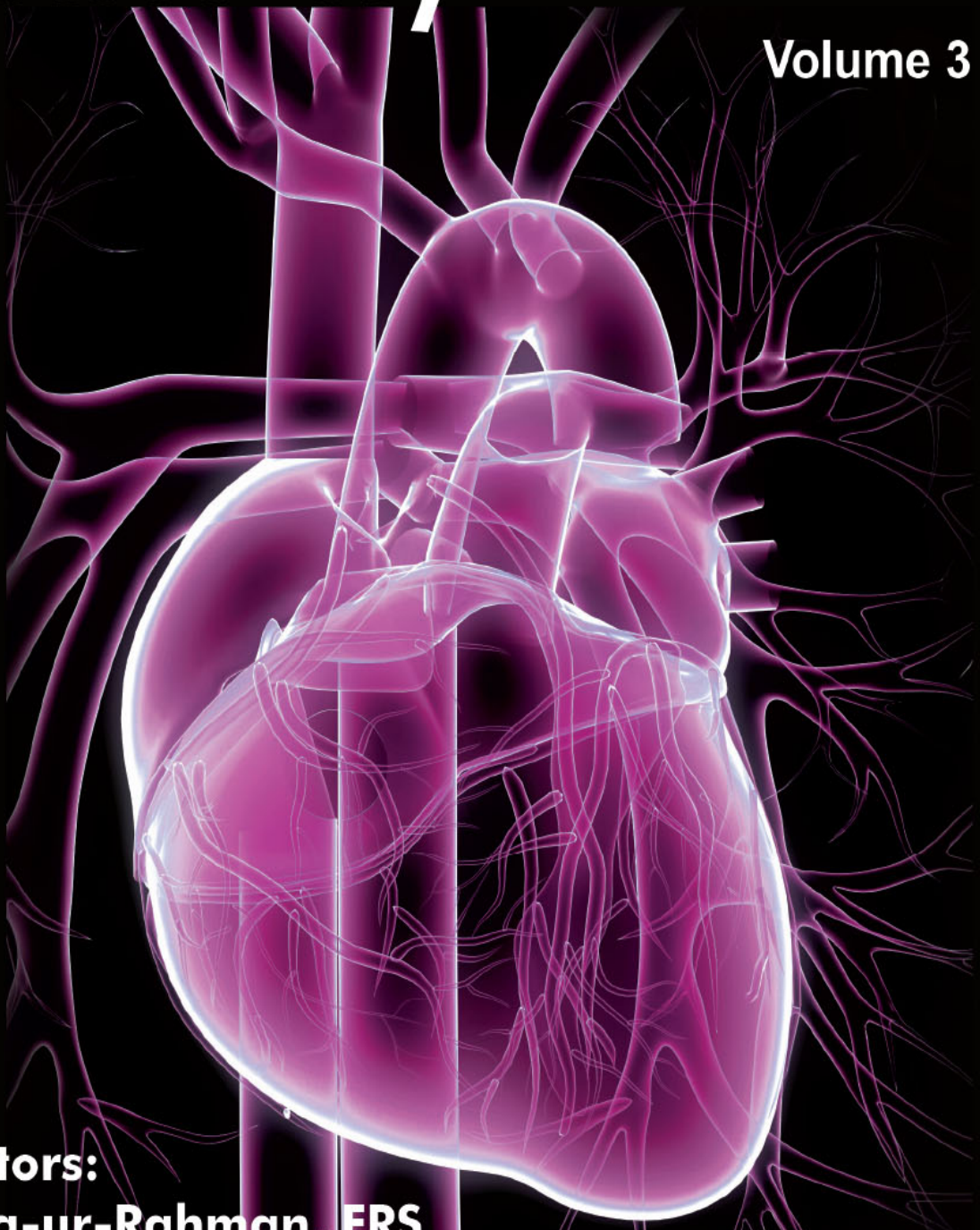

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Frontiers in Cardiovascular Drug Discovery

(Volume 3)

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PREFACE

Cardiovascular diseases are the major cause of morbidly and mortality in humans. Despite major advancements in cardiovascular drug discovery and development, heart diseases and stroke remain the leading public health concern and primary causes of death globally. The development of effective and safe medicines that control blood pressure and cholesterol has significantly reduced the death rate from heart diseases. However, with global rise in metabolic disorders and aging populations, the prevalence of hypertension, high cholesterol, and diabetes is increasing. Heart diseases and stroke are becoming a worldwide pandemic as developing nations are witnessing the increasing health burden caused by them. To tackle this problem, tremendous research work has been conducted to understand the cause of cardiovascular diseases at molecular levels. This has led to the identification of new drug targets which are now vigorously studied.

The 3rd volume of the ebook series, "*Frontiers in Cardiovascular Drug Discovery*" comprises six comprehensive reviews, contributed by leading experts in these fields. Each review is focused on a certain important aspect of cardiovascular drug discovery and development, including the identification of new molecular targets and the outcome of clinical studies.

Boukhris *et al.* have contributed a review on $P2Y_{12}$ receptor antagonists as efficient treatment of platelet dysfunctions, including platelet aggregation and thrombus formation. The authors have comprehensively reviewed the role of $P2Y_{12}$ receptors in thrombus formation, and the mechanism of action of various classes of $P2Y_{12}$ receptor antagonists as anti-platelets agents. They also present the literature pertaining to the clinical outcome of efficacy and safety of various new generation of anti-platelet drugs, as well as prospects of tailored or individualized anti-platelet therapy for improving the clinical outcome.

Various forms of acute heart failures are heterogeneous in nature. They are difficult to manage and the conditions are often difficult to treat. The development of pharmacotherapy of acute heart failures has been comprehensively reviewed by Panjrath *et al.* in Chapter 2. The authors review the various classes of drugs and their contributions in reducing the mortality due to acute heart failure. The development of new therapeutic agents under the new regulatory requirements is also discussed, along with potential future developments in heart failure management and treatment.

Amit Agrawal reviews the role of vasopressin (arginine vasopressin) in cardiovascular health. Vasopressin is an anti-diuretic hormone which performs many essential functions in the body including maintaining plasma osmolality and volume. It has a direct impact on cardiovascular functions. A key function of AVP in the body is to regulate the extracellular fluid volume by

regulating the renal handling of water. Vasopressin acts on renal collecting ducts *via* V_2 receptors to increase water permeability (cAMP-dependent mechanism), which leads to decreased urine formation and thus increases the blood volume, cardiac output, and arterial pressures. Over the years, synthetic vasopressin has emerged as an important drug for the treatment of various shock states. The author has elegantly reviewed various uses of vasopressin in critical care, especially in the treatment of vasodilatory shock. The commentary on mechanism of action of vasopressin at molecular and receptor levels provides insight into the action of this smart drug which is finding new uses with every passing day.

Cerebral small vessel disease (CSVD) or microangiopathy is a group of diseases involving microangiopathy and unspecific arteriopathy. This is a common risk factor for cognitive impairment, characterized by hypertrophy, vascular modification, and endothelial dysfunction that alter cerebrovascular functions, and auto-regulation of cerebral blood flow. CSVDs increase the risk of ischemia and tissue bleeding and may be categorized into six classes, based on the tissue types that they affect. The review by Alvarez-Parez focuses on type 1 CSVD, which is among the most common conditions, also called arteriolosclerosis. It is associated with aging, arterial hypertension, and diabetes. The author reviews the literature on the etiology and treatment of type 1 CSVD. Various classes of anti-aggregant drugs (aspirin, ticlopidine, and aspirin plus other drugs) have shown efficacy in this condition. The results of clinical studies on various classes of drugs have been discussed in this excellent review.

Shagdarsuren *et al.* have contributed a review on recent developments on a novel class of therapeutic agents which block and disable the complement blocking system. The complement cascade is an integral component of the body's innate immune system, which boosts the capacity of antibodies and phagocytic cells to clear the invading microorganisms and damaged cells from the body. The complement system is involved in promoting inflammation in various pathological conditions. Most importantly, the complement cascade is known to be involved in obesity, fatty liver, diabetes and cardiovascular diseases (CVD). The complement system comprising several complex small proteins and their receptors, is known to be activated in cardiovascular diseases. This has attracted major scientific interests in various complement molecules /components as new therapeutic targets. The authors present an excellent commentary on various complement molecules, their primary and secondary receptors, and their functional roles in the onset and progression of CVDs. They have also summarized the beneficial results observed in various pre-clinical studies conducted on targeting of specific components of the complement system in CVD animal models. This new class of drugs which includes gene targeting agents, neutralizing antibodies, and small molecular inhibitors, holds great promise for the treatment of CVDs in future.

Antiplatelet and anticoagulant therapies are essential parts of cardiovascular and cerebrovascular diseases prevention and management. They are among the most difficult

classes of therapies, where balancing the benefits of antiplatelet and anticoagulant drugs with the risk of gastrointestinal and other bleedings is a major challenge. Aspirin and warfarin have been the most frequently used medicines for this purpose, with high risks of bleeding, and other therapeutic limitations. Recently, several novel classes of antiplatelet and anticoagulant agents have been developed which specifically target the mechanism of coagulation pathways, and thus have improved therapeutic efficacy. These new drugs are also associated with the occurrence of bleedings, including gastrointestinal bleeding. Johnson *et al.* have reviewed the recent literature on the pharmacology of available antiplatelet and anticoagulant drugs, particularly with reference to the associated risks, such as gastrointestinal bleeding and toxicity. They have also provided data about currently available and in pipeline anticoagulant reversal agents. This review is therefore an excellent source of information about the merits and demerits of new antiplatelet and anticoagulant agents, as well as development of agents which can reverse the bleeding episodes as a result of anticoagulant therapies.

The editors wish to express profound gratitude to all the contributors for the timely submission of their review articles for the 3rd volume of the eBook series. We also appreciate the efforts of the entire team of Bentham Science Publishers for efficient processing. The efforts of Mr. Omer Shafi (Assistant Manager Publications), Mr. Shehzad Naqvi (Manager Publications) and team leader Mr. Mahmood Alam (Director Publications) for their assistance in putting together an excellent compilation of well written articles in this important field of biomedical research. We sincerely hope that this volume will receive wide appreciation from readers.

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CHAPTER 1

P2Y12-Receptor Antagonists and the Concept of Tailored Strategy

Marouane Boukhris[1,2,*], Salvatore D. Tomasello[1], Zied Ibn Elhadj[2] and **Alfredo R. Galassi[1]**

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Abstract: Platelet represents the cornerstone of both physiologic hemostasis and thrombosis acting *via* different pathways. Adenosine diphosphate (ADP) plays a crucial role in platelet activation and thrombus formation through its interaction with platelet P2Y12 receptor, making therefore this receptor an interesting therapeutic target for anti-thrombotic agents.

Around the world, millions of people affected by coronary artery disease are treated with anti-platelet agents. Indeed, dual anti-platelet therapy, consisting of a combination of aspirin and a P2Y12 receptor antagonist, is the recommended strategy in patients with acute coronary syndrome and those who underwent percutaneous coronary intervention with stent implantation. Furthermore, the introduction of different generations of P2Y12 receptor antagonists has immensely improved the clinical outcome, as well established through literature.

Although the concept to replace "one size fits all" paradigm to a more individualized approach in anti-platelet therapy seems to be rational, in the area of based evidence medicine, a clear prognostic impact of such a strategy is not yet clearly demonstrated.

In the current chapter, we tried to summarize the mechanisms of P2Y12 receptor antagonists anti-platelet action, to report clinical proofs regarding the efficacy/safety of

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new generations of this class of drugs, and to discuss the place of a tailored strategy and its impact on improving clinical outcome.

Keywords: Anti-aggregation therapy, Bleeding, Cangrelor, Clinical outcome, Clopidogrel, Coronary artery disease, Dual anti-platelet therapy, Elinogrel, Genetic testing, High on-treatment platelet reactivity, Ischemic event, Low on-treatment platelet reactivity, Percutaneous coronary intervention, Platelet aggregation, Platelet reactivity, Prasugrel, P2Y12 receptor, P2Y12 receptor inhibitors, Stent implantation, Ticagrelor.

INTRODUCTION

The primary function of platelets is to preserve vascular integrity and hemostasis; however, in presence of vascular disease, particularly atherosclerosis, this normal process can become excessive, leading to thrombotic events. The role of platelets in the pathophysiology of arterial thrombosis has been investigated over the past decades and established as crucial [1 - 3]. Platelet-dependent thrombotic events such as myocardial infarction (MI), stroke and even sudden cardiac death, often started by an acute plaque destabilization followed by platelet adhesion, activation and aggregation, which represented the key processes. Indeed, differently from normal endothelium platelets only adhere to disrupted endothelial surfaces. Thereafter, platelets undergo shape change, secrete the contents of their granules, transform endogenous arachidonic acid into thromboxane A2, and aggregate with one another, resulting in a platelet-dependent thrombus [2, 3].

Aspirin represents the first effective platelet inhibitor drug used in humans. It results in an irreversible modification of the enzyme cyclo-oxygenase preventing it to convert arachidonic acid into thromboxane A2 [4].

On the other hand, adenosine diphosphate (ADP) also plays a capital role in platelet activation. Originating from platelet dense granules, red blood cells and damaged endothelium, its interaction with platelet receptors (particularly P2Y12 receptors), leads to an activation-amplification cascade resulting in thrombus formation [5]. This capital role of ADP makes it an appropriate therapeutic target for anti-platelet agents acting differently from aspirin. In this respect, P2Y12 receptor antagonists had been introduced in cardiovascular diseases (Fig. **1**).

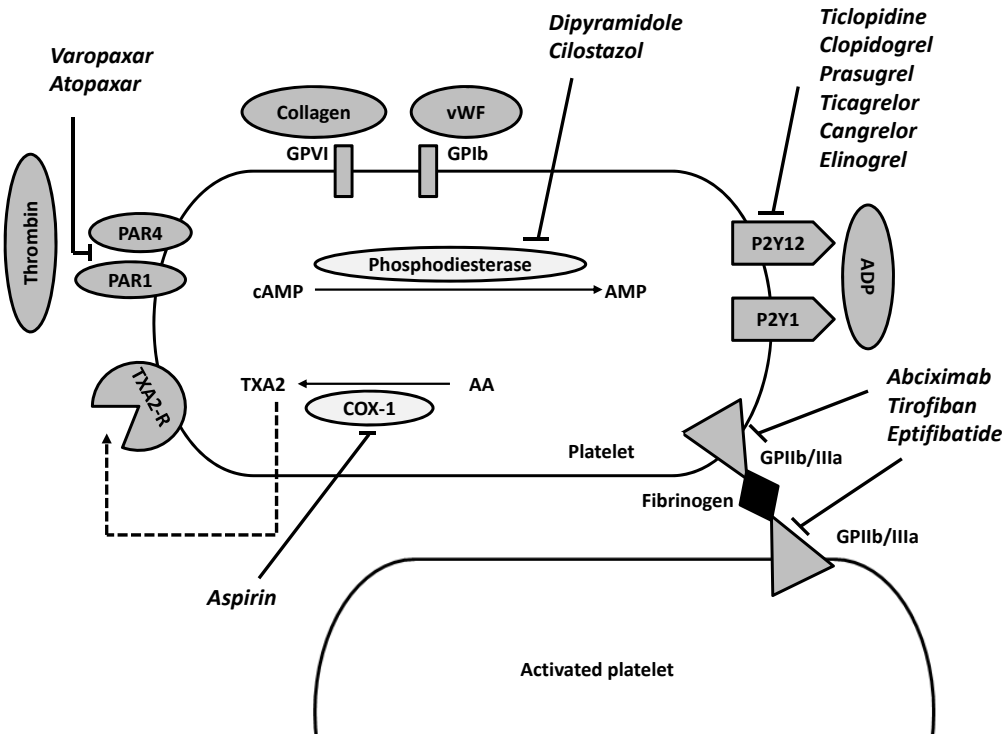

Fig. (1). Platelet activation and the mechanism of action of different anti-platelet agents.

Nowadays, around the world, millions of people affected by coronary artery disease (CAD), are treated with antiplatelet agents. Indeed, dual anti-platelet therapy (DAPT), consisting of a combination of aspirin and a P2Y12 receptor antagonist is the recommended strategy in patients with acute coronary syndrome (ACS) and those who underwent percutaneous coronary intervention (PCI) with stent implantation [6]. Furthermore, the introduction of new generations of P2Y12 receptor antagonists has immensely improved the clinical outcome,

During the last decade, the interest in platelet reactivity testing has grown, with the aim to obtain a tailored and personalized anti-aggregation strategy. However, the prognostic impact of such an approach remains not yet clearly demonstrated.

In the current chapter, we tried to summarize the mechanisms of P2Y12 receptor antagonists anti-platelet action, to report clinical proofs regarding the

CHAPTER 2

Evolution of Heart Failure Pharmacotherapy

Gurpreet Sodhi, Ju Kim, Stephen Robie and **Gurusher Panjrath***

Department of Medicine (Cardiology) and Heart and Vascular Institute, The George Washington University School of Medicine and Health Sciences, Washington D.C., USA

Abstract: Heart Failure is a chronic disease with increasing prevalence around the world. It is associated with significant mortality, morbidity, and healthcare costs. Over the past 2-3 decades, major advances in drug development have contributed significantly in decreasing mortality among those with chronic systolic heart failure. However, similar advances are missing in patients experiencing acute heart failure and heart failure with preserved ejection fraction. In the current chapter, we will review the historical development of pharmacotherapy in heart failure medical management. A comparative review of contribution of each class towards reducing mortality will be performed. More importantly, drugs which failed to succeed or impact significantly will be reviewed and an insight on why they may have failed will be provided. Development of new drugs is limited by regulatory requirements as well as disease heterogeneity. New agents under development will be summarized and mode of their action will be detailed. This chapter aims to serve as a comprehensive resource on strategies both past and current as well as provide discussion regarding potential future developments in heart failure pharmacotherapy.

Keywords: ACE inhibitors, Aldosterone antagonists, Beta blockers, BiDil, Diastolic dysfunction, Digoxin, Diuretics, Dobutamine, Heart decompensation, Heart failure, History, Ibopamine, Ivabradine, Milrinone, Natriuretic peptides, Novel therapies, Pharmacology, Statin, Systolic dysfunction, Vasodilator.

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INTRODUCTION

The collection of symptoms that are regarded as the syndrome of 'congestive heart failure' have been reported since the era of Hippocrates, who made note of the physical signs of pulmonary congestion: 'When the ear is held to the chest, and one listens for some time, it may be heard to see the inside like the boiling of vinegar' [1]. From the beginning, disordered fluid balance was a key component to the clinical understanding of what would develop into congestive heart failure. As our understanding of heart failure and the complexity of the body's response has evolved, so has the development of pharmacologic treatment. To understand the evolution of therapeutic treatment options, one must appreciate the development of our understanding of the disease itself.

When viewing the progression of heart failure therapeutics retrospectively, one may successfully divide our understanding of the disease etiology into three general models: cardiorenal, cardiocirculatory, and neurohormonal [1]. Of course, these models came into play when it was clear that the heart was indeed the center of pathology. This concept was not entirely clear for several centuries [1]. Until Harvey's revelation regarding circulation, the physiologic function of the heart was not entirely well understood [1, 2]. Thus, the concept of disordered fluid balance, independent of the crucial role played by the heart and the cardiovascular system, with the accompanying symptoms of swelling and shortness of breath, dominated pathophysiologic understanding for several years [1].

As our initial understanding of the disease process focused upon the outward symptomatic manifestations of heart failure, symptomatic relief was focused on the management of anasarca or, as it was so commonly referred to, 'dropsy' [1]. Volume control at any cost was the predominate concentration of treatment. The focus on the volume sequelae of congestive heart failure is a predominant focus of the 'cardiorenal' model of heart failure. Hence, the earliest attempts at pharmacologic therapy would attempt to manipulate this pathophysiologic pathway [1]. Medications were primarily judged on their ability to reduce total body volume. This was often done with no clear understanding of the drugs' true mechanisms of action or effects. Treatments such as foxglove (modern day Digitalis) were uti-lized on the observation of their therapeutic effects with little

appreciation for their underlying machinations [2]. Diuretics, in some primitive form or another, were utilized with great frequency. Prior to their advent, reduction in circulating volume, whether *via* diaphoretics, purgatives, or direct blood letting, were commonplace [1, 3]. Some attempts to reduce swelling even went so far as to utilize external mechanical measures such as 'congesting cuffs', the practice of applying tourniquets to the peripheral extremities, in an attempt to capture volume in the periphery and decrease pulmonary pressures [3]. These efforts were not necessarily due to poor scientific approach persay. Indeed, they often made sense given the limited understanding of pathophysiology at the time. However, work clearly needed to be done to move beyond the simplistic external observations that initially drove the cardiorenal era.

The concept of 'dropsy of the chest' came into view during the 17th century [3]. The heart's role was not widely regarded in the syndrome until vivisection became more prevalent and an understanding of structural heart disease developed in the 18th century [1, 3]. A clear differentiation of cardiac and renal etiologies were developed by John Blackall and Richard Bright during this time period [3]. Though there existed primitive manifestations of modern medications such as foxglove, therapies up to the advent of the second world war were frequently of limited therapeutic benefit and had a high index of toxicity [4, 5]. The earliest forms of diuretics had high toxic potential and commonly included the use of organic mercurials [4]. Primitive diuretics provided much needed symptom relief but the natural history and progression of heart failure, their mechanisms and existence not quite characterized at this time, were not impeded by these therapies [1, 3, 4]. As such, researchers continued to search for additional theoretical models that explained not only symptom development, but also disease progression.

In 1833, Bertin was one of the first to note that dilatation 'weakens the contractile power of the muscular substance', but the direct correlation with dropsy remained elusive [1]. Still, this focus on the structural consequences upon the heart in congestive heart failure was tantamount. With the prevalence of rheumatic heart disease and infectious valvulopathies like syphilis, the initial understandings of heart failure pathology were limited largely to structural heart disease [1, 6]. In the first half of the 20th century, nearly three quarters of all heart disease in

CHAPTER 3

Vasopressin and the Cardiovascular System: Receptor Physiology and Clinical Implications

Amit Agrawal*

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Abstract: Arginine vasopressin or antidiuretic hormone has got name "vasopressin" due to its vasoconstrictor properties. Vasopressin is a posterior pituitary hormone which is essential for the cardiovascular homeostasis. In normal physiological conditions, it helps in regulation of plasma osmolality and volume *via* its action on the kidney. Other important actions of vasopressin include regulation of vascular smooth muscle tone, control of circadian rhythm, thermoregulation, and adrenocorticotropic hormone release (ACTH).

In recent years, vasopressin has emerged as an important therapeutic option in the treatment of various shock states. Vasopressin has increasingly been used in both pediatric and adult critical care units for the management of central diabetes insipidus, bleeding abnormalities, oesophageal variceal haemorrhage, asystolic cardiac arrest, and various shock states *e.g.* shock due to ventricular fibrillation, hypovolaemia, sepsis and cardiopulmonary bypass.

Ongoing researches helped in increasing understanding of the endocrine response to shock and importance of vasopressin in their management. Prolonged vasodilatory shock is characterised by relative deficiency of endogenous vasopressin and marked vasopressor effects of the exogenously administered hormone. Sepsis and post cardiopulmonary bypass conditions are the most common causes of vasodilatory shock; however, vasodilation can be a common final pathway of any type of shock. Unlike other vasoconstrictors, vasopressin also exerts some vasodilatory properties which can be due to its action on various receptors, namely V1 vascular, V2 renal, V3 pituitary and oxytocin receptors, and the P2 purinergic receptors producing variable and seemingly contradictory responses.

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To better understand the variable responses on the vascular system, which vasopressin exerts, it is prudent to acquire the knowledge of the physiology and action of the different vasopressin receptors. In this chapter, vascular actions of vasopressin along with distribution of the classic vasopressin receptors and signalling pathways will be explored.

Keywords: Arginine-vasopressin, Oxytocin receptors, Terlipressin, Vasopressin, Vasopressin receptors.

INTRODUCTION

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is one of the first described and structurally characterized neuropeptide hormones. Vasopressin plays an important role in many peripheral and central functions such as regulation of plasma osmolality and blood pressure through its peripheral actions, and central actions include memory, learning and stress-related disorders. Vasopressin is an important stress hormone that has both vasoactive as well as antidiuretic properties. Since its isolation and synthetic preparation vasopressin has been extensively studied, mainly to treat diabetes insipidus and variceal hemorrhage. The vasoactive properties of vasopressin have become an area of intense research when Landry and colleagues first reported a relative deficiency of vasopressin in septic shock and increase in blood pressure and urine output after infusion of low doses of vasopressin [1, 2]. Now, vasopressin has emerged as an important therapeutic option in the management of septic shock and vasodilatory shock from other causes [3 - 5].

Since its isolation, vasopressin has been extensively studied and found to be useful in the management of enuresis, variceal bleeding, septic shock, and cardiac arrest. Enormous work has been done to demonstrate the complex system of synthesis, storage, secretion and regulation of vasopressin, in addition to its many different functions on specific receptors distributed throughout the body in such a manner as to perform its main effects, the regulation of plasma osmolality and arterial blood pressure, in harmony with several other hormones. However in this chapter, only those clinical uses of vasopressin implicated in cardiovascular homeostasis will be discussed. The initial part will cover the physiology and pharmacology of the hormone including structure and distribution of vasopressin

receptors and their signalling pathways as it is necessary to understand the seemingly paradoxical vasodilatory and vasoconstrictor actions of vasopressin. In the later part of the chapter, the mechanisms of action of vasopressin through different types of receptors leading to vasoconstriction or vasodilation of vascular smooth muscles will be discussed.

HISTORICAL ASPECTS

Vasopressin was first discovered by Oliver & Schafer in 1895 by observing the vasoconstrictor effect of an extract of the posterior pituitary [6]. Human vasopressin contains the amino acid arginine; therefore, it is also named as "Arginine Vasopressin". In 1906, Sir Henry Dale has discovered another pituitary hormone "oxytocin" by successfully demonstrating the contractions of the mammalian uterus by a component of the pituitary [7]. A few years later in 1913, Farini in Italy and von del Venden in Germany successfully treated the patients of diabetes insipidus by injection of neurohypophysis extract and independently demonstrated its antidiuretic effect [8, 9]. In 1951, Turner *et al.* succeeded in purification of vasopressin preparation and identified the nine amino acid sequences of vasopressin [10]. Two years later in 1953, Acher & Chauvet and du Vigneaud *et al.* proposed the structure of vasopressin [11, 12]. Very soon, the structure of related oxytocin was also identified by Tuppy and du Vigneaud *et al.* [13, 14]. In 1954, du Vigneaud *et al.* first synthesized the vasopressin in a laboratory and proved that both the vasopressor and antidiuretic effects were from the same hormone [15]. For this pioneering work, du Vigneaud also won the Nobel Prize in chemistry in 1955.

Following discovery of structure and amino acid sequences of vasopressin and oxytocin, attention of the researchers have turned to locate the site of synthesis of these hormones in human body. About a decade later, Sachs *et al.* in their studies demonstrated the hypothalamus as the site of synthesis of vasopressin and oxytocin and that from the hypothalamus these hormones are transported to the posterior pituitary [16 - 18]. Pioneering studies by Howard Sachs and his colleagues hypothesized that the vasopressin peptide was formed by the post-translational processing of a precursor protein [16 - 17]. Gainer and colleagues confirmed their hypothesis by reporting the first physical evidence for the

CHAPTER 4

Cerebral Small Vessel Disease: A Clinical Review Focusing on Therapeutic Strategies

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Abstract: The term cerebral small vessel disease (CSVD) or microangiopathy includes several pathological processes of different aetiologies which cause an increase of wall thickness (basically the basement membrane), a narrowing of the lumen, and a weakening of walls in arterioles, capillaries and venules. These vascular modifications cause a loss of proteins towards the interstice and a slowness of blood flow, increasing the risk of ischemia and tissue bleeding.

The CSVD may be aetiopathogenically classified in 6 types. The CSVD type 1, called arteriolosclerosis, is the most prevalent form and has a 6 to 10 times higher prevalence than stroke. It is related to aging and classical vascular risk factors, like arterial hypertension and diabetes mellitus. This review will focus on type 1 CSVD.

In the brain, the main pathological findings are loss of smooth muscle cells in the media, accumulation of fibrohyaline material, fibrinoid necrosis, and development of microatheromas and Charcot-Bouchard microaneurysms. The parenchymatous consequences of these vessel modifications are both ischemic (white matter lesions, lacunes) and haemorrhagic (microhaemorrhages, intracerebral haemorrhages). The clinical manifestations of arteriolosclerosis include cognitive deterioration, dementia, mood disorders, gait and motor disturbances, lacunar strokes, and disability. *In vivo*, the diagnosis of CSVD is supported by neuroimaging findings (lacunes, leukoaraiosis, white matter lesions, microhaemorrhages), especially by use of magnetic resonance techniques. The role of other biomarkers (plasma and cerebrospinal fluid biochemical parameters, resistance indexes in transcranial Doppler study) is not completely defined.

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In patients with diagnosis of microangiopathy there are three main therapeutic considerations. First, there are specific risks in these patients during standard clinical management of acute ischemic stroke. Several studies showed an increased risk of intracranial bleeding related to thrombolytic therapy for acute stroke and anticoagulant treatment for secondary prevention. Indeed, the presence of leukoaraiosis raised the probability of peri-operative stroke or death in patients who underwent carotid endarterectomy. Second, the symptomatic management of patients with cognitive impairment related to CSVD, which is currently based on memantine and acetylcholinesterase inhibitors used in Alzheimer's disease. Third, the specific therapy directed to vessel pathology and parenchymatous consequences (secondary prevention). Available data support the use of antiaggregant drugs to reduce the risk of recurrence of lacunar strokes. Aspirin, ticlopidine, aspirin plus clopidogrel, dipiridamol plus aspirin, and cilostazol showed efficacy in this subtype of stroke. The optimal control of arterial pressure and cholesterol level also reduces the risk of stroke, independently if mechanism of disease was macro or microvascular. However, the specific drugs and the optimal goals are not defined and ongoing trials are trying to evaluate different drugs and preventive strategies (cilostazol plus aspirin, aggressive versus standard blood pressure control). Considering the specific treatment of vascular pathology, there are few available data. Experimental studies showed that relaxin may increase the arterial distensibility. In humans, one ongoing trial is investigating the efficacy and safety of an anti-amyloid beta monoclonal antibody in patients with probable cerebral amyloid angiopathy (CSVD type 2).

Keywords: Acetylcholinesterase Inhibitors, Antiaggregants, Cerebral Amyloid Angiopathy, Cerebral Microangiopathy, Cerebral Microhaemorrhages, Cerebral Small Vessel Disease, Deep Brain Infarcts, Deep Intracerebral Haemorrhages, Enlarged Perivascular Spaces, Lacunar Stroke, Memantine, Vascular Dementia, White Matter Lesions.

CONCEPT OF CEREBRAL SMALL VESSEL DISEASE

The small vessel diseases are mainly systemic disorders that may affect different organs and areas of the body. In some conditions, the brain can be the main or only target of the disease, but in other disorders the nervous system might not be affected at all. The term cerebral small vessel disease (CSVD) includes the pathological processes affecting small arteries, arterioles, capillaries, and small veins of the brain. These processes increase the wall thickness, reduce the vascular lumen, and cause structural weakness. The parenchymatous results are

both ischemia and haemorrhage [1]. Therefore, the presence of CSVD is associated with a higher risk of developing ischemic and haemorrhagic stroke, cognitive decline, gait disturbances and dementia. Because the small vessels cannot be visualized *in vivo* and only indirect manifestations may be assessed, the most accepted biomarker of CSVD is the presence of white matter lesions, lacunar infarcts, subcortical atrophy, and haemorrhagic lesions on magnetic resonance imaging (MRI) [2].

The extremely high prevalence of CSVD implies that all disorders associated with this pathology represent an important issue for health systems. Cerebral small vessel disease is the basis for nearly 30% of all ischaemic strokes, it is the first cause of vascular dementia, and it probably is the second cause of dementia syndrome and age-related cognitive decline [3].

Currently, the therapeutic approaches to CSVD are a preventive strategy, based on control of some modifiable risk factors, and a symptomatic control of some clinical manifestations. More specific or "curative" treatments are not available.

ANATOMY OF CEREBRAL SMALL VESSELS

The small vessels are penetrating vessels which vascularise the cerebral and cerebellar cortices, deep white matter, basal nuclei, and brain stem. These vessels originate from the circle of Willis, the system formed by the middle, anterior, and posterior cerebral arteries, the basilar artery, and the anterior and posterior communicating arteries. Classically, two kind of penetrating arteries originate from the circle of Willis: central, ganglionic or deep, and cortical, circumference or superficial [4].

Central System

The vessels of the central system emerge from the own circle and the first segment of main cerebral arteries to penetrate perpendicularly into the parenchyma. They consist of: (1) lenticulostriate arteries, originated from the middle and anterior cerebral arteries to irrigate diencephalon, striate and anterior arm of the internal capsule; (2) thalamo-perforating branches, originated from the posterior cerebral artery to irrigate the thalamus. The anterior and posterior

CHAPTER 5

Complement Blocking Therapeutic Strategies: A Prospective Approach for the Treatment of Cardiovascular Diseases

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Abstract: Despite huge improvements in clinical diagnosis as well as numerous options in patient care and treatment, the incidence of cardiovascular disease (CVD) has been on the rise in the last decade potentially due to hitherto deteriorating lifestyle. As a chronic inflammatory response of the arterial vessel wall, atherosclerosis and its clinical sequelae such as coronary heart disease, cerebrovascular disease and peripheral artery disease continue to be the leading causes of morbidity and mortality worldwide. This makes it necessary to explore novel therapeutic strategies to control and manipulate the mediators of atherosclerosis and cardiac repair processes in order to help combat cardiovascular events. The complement system, an important part of the innate immune response, constitutes a complex network of plasma proteins and membrane cofactors which act in concert with other immunological systems of the body for a rapid defense against foreign intrusions and infections. Activation of the complement cascade in CVD is well established. Numerous well-conducted studies on

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targeting specific components of the complement cascade in CVD have opened avenues for targeted pharmacological inhibition of the complement system at different levels of complement activation. The use of gene targeting and neutralizing antibodies as well as small molecule inhibitors in animal models of human CVD has provided a clear beneficial role for blocking complement C5, C5a, C5a receptor (C5aR1, CD88) and the soluble complement receptor 1 (sCR1) and different regulators at C3 convertase level. Moreover, the discovery of the second receptor for C5a, the C5aR2 (C5L2, C5a receptor-like 2) and recent studies on the functional role in atherosclerosis has raised the intriguing possibility of the use of this receptor as a novel anti-inflammatory strategy. Though work is still in progress to determine whether there is a global effect of this receptor in pathogenesis of cardiovascular disease, there is no doubt that complement blocking strategies is an emerging field in medical pharmacology.

Keywords: Atherosclerosis, Cardiac and vascular remodelling, Cardiovascular disease, Complement inhibitors, Complement system and activation, Myocardial infarction.

Cardiovascular disease (CVD) is the leading cause of death worldwide and the underlying pathological condition has been primarily attributed to atherosclerosis. It is well established that atherosclerosis is a chronic inflammatory process of the arterial vessel wall orchestrated by variety of mediators of innate and adaptive immunity [1, 2]. As a major and crucial component of both innate and adaptive immune system, the complement system maybe envisioned to have a pivotal role in the pathomechanisms of CVD. Indeed, substantial evidence supports complement-mediated pathogenesis of CVD through pleiotropic effects on multiple cell types strongly implicated in CVD [3, 4]. Several components of the complement system have been strongly associated with the outcome of cardiovascular events in patients [5 - 8]. Employing *in vitro* mechanistic studies and diverse *in vivo* models that mimic human CVD, the functional role of complement components in CVD has been established. In line with its well characterized pro-inflammatory effects, function in immune complexes and debris as well as apoptotic cells removal, the activation of the complement system has both beneficial and detrimental effects. Several studies using gene targeting, neutralizing antibodies and small molecule inhibitors have helped in identifying specific complement components harboring therapeutic potential. In this chapter,

we discuss both established and emerging paradigms in complement-mediated mechanisms underlying CVD. We summarize naturally occurring complement inhibitors and regulators, at various levels of complement activation, which could be harnessed for the treatment of CVD.

1. COMPLEMENT ACTIVATION CASCADE AND PATHWAYS

Complement system was first reported in 1896 by Jules Bordet, who found that antibodies present in fresh serum assisted in bacterial killing, but serum heated at 56°C or higher lost this property [9, 10]. The complement system, part of the innate and adaptive immune system, is usually regarded as the primary host-defense mechanism against pathogenic infections [11, 12]. This system is considered to be part of the primitive defense mechanism coordinating innate and adaptive immune systems [11, 13]. The mammalian complement system consists of more than 50 circulatory and membrane bound proteins. These proteins aid in differentiating between host and pathogen. Once a foreign body is detected by these proteins, they interact with one another and form immune complexes thereby aiding in pathogen clearance [14, 15]. The complement cascade can be activated by at least three major pathways - 1) Classical pathway 2) Lectin pathway and 3) Alternate pathway [16, 17]. The simplified version of the three pathways is depicted in Fig. (**1**). Additionally, the proteolytic enzymes in the newly described extrinsic protease pathway cleave C3 and C5 independent of conventional convertases. Furthermore, a new activation pathway exists for generation of C5a, especially in the absence of C3, with thrombin acting as a potent C5 convertase [16].

1.1. Classical Pathway of Complement Activation

The classical pathway of complement activation has always been regarded as the primary responder (major effector) to various stimulants such as Fc portion of immunoglobulin (Ig) in antigen-antibody complexes, enzymes like trypsin and numerous endotoxins, cell membranes, viruses and a string of other external stimulants [18]. It is the only complement pathway with functions in the adaptive immune system [19]. The classical pathway is activated when antibodies from pathogens are recognized and bound to multiple sites on the cell surface,

CHAPTER 6

New Antiplatelet and Anticoagulant Agents: Towards Recognition and Reduction of Gastrointestinal Harm

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Abstract: The most important adverse effect of antiplatelet and anticoagulant therapy is the occurrence of bleeding. Gastroenterologists, cardiologists, and primary care physicians often find themselves balancing the benefits of antiplatelet and anticoagulant therapy with the risk of bleeding, namely gastrointestinal bleeding. While aspirin and warfarin have long been the mainstay of oral antiplatelet and anticoagulant therapy, respectively, recent discoveries of more precise targets for therapy have come to market in order to reduce the risk of cardiovascular events and overcome the well-known limitations that plague warfarin therapy (*e.g.* narrow therapeutic index, variable individual metabolic response, and numerous food and drug interactions). Despite the fact that these novel agents may increase the risk of gastrointestinal bleeding [1], their ease of use makes them more attractive than conventional agents. This review will provide an overview of the pharmacology of available antiplatelet agents and anticoagulants, outline risks that clinicians should be cognizant of when considering prophylactic therapy in order to reduce the risk of gastrointestinal toxicity, and provide up to date data on reversal agents that are currently available as well as those that are in the pipeline.

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INTRODUCTION

Gastrointestinal bleeding (GIB) is a known adverse effect of antiplatelet agents [2]. and anticoagulants [1]. with significant morbidity and mortality in addition to an enormous burden on global health care resources [3]. The mean hospital cost for an episode of upper GIB, lower GIB, or small-bowel bleeding is upwards of $7,300 USD, $4,800 USD, and $40,000 USD, respectively [3]. Expanding indications and ease of use have made antithrombotic therapy robust, which in turn has increased the burden of GIB related to these agents [4]. Antiplatelet agents (*e.g.* aspirin and thienopyridines) cause ulcers and erosions by inhibiting cyclooxygenase (COX)-1 resulting in prostaglandin depletion, which plays a pivotal role in maintaining the gastric epithelium [5]. In addition, antiplatelet agents impair angiogenesis and these two mechanisms in concert are thought to result in GIB. Traditional anticoagulants and novel oral anticoagulants (nOACs) (*e.g.* direct thrombin inhibitors or factor Xa inhibitors) are thought to precipitate bleeding from pre-existing lesions [1]. The nOACs may even predispose susceptible patients to a higher rate of GIB than traditional anticoagulants. Both of the landmark trials (Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) [6] and Rivaroxaban *versus* Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) [7]) that established the relative efficacy/non-inferiority of dabigatran and rivaroxaban, respectively, compared with warfarin therapy in selected patients demonstrated there to be an increased risk of GIB with these agents compared to warfarin therapy. Here, we review the pharmacology of available antiplatelet and anticoagulants, both traditional and nOACs, outline risk factors that warrant prophylactic therapy in order to reduce the risk of gastrointestinal toxicity, and review the most up to date literature on reversal agents that are currently available as well as those that are in the pipeline.

PHARMACOLOGY OF AVAILABLE ANTIPLATELET AGENTS

Aspirin

Aspirin irreversibly inhibits both COX1 and COX2 *via* serine acetylation. Aspirin achieves its antiplatelet properties through its effects on COX1-mediated thromboxane A2, which is highly sensitive to aspirin [8]. Higher doses are

required for aspirin to exhibit its anti-inflammatory *via* inhibition of COX-2 mediated prostaglandin I2 generation, thus larger daily doses at shorter dosing intervals are necessary in order to achieve its anti-inflammatory effects [8 - 10]. Fig. (**1**) depicts how differing doses of aspirin effect the COX pathway.

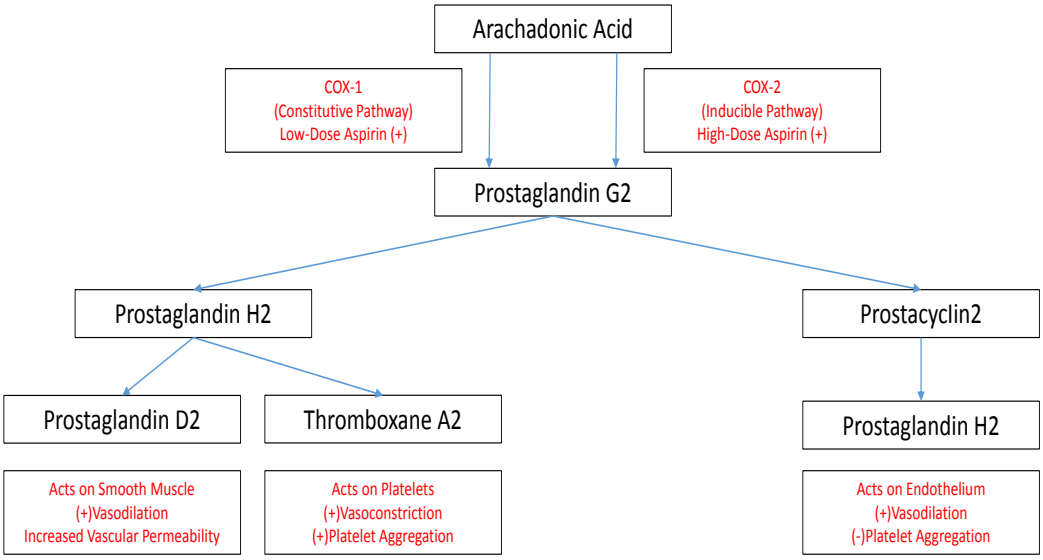

Fig. (1). Effect of differing doses of aspirin on the COX pathway.

Aspirin reaches its peak plasma concentrations within 40 minutes of ingestion, with notable platelet inhibition occurring within 1 hour [8]. Enteric-coated formulations have delayed onset, with peak plasma concentrations occurring within 4 hours after ingestion. Despite having a relatively short half-life of only 15 minutes, the effect of aspirin on platelets last for the entire lifespan of the platelet due to irreversible inhibition [8]. In addition, studies have also shown aspirin to effect COX1 on megakaryocytes (platelet precursors) thus affecting newly released platelets in addition to pre-existing ones [8, 10].

Thienopyridines– Clopidogrel, Prasugrel, and Ticagrelor

The thienopyridines and its derivatives are a group of antiplatelet agents that

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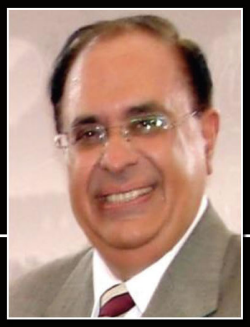

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Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1020 international publications in several fields of organic chemistry including 727 research publications, 37 international patents, 68 chapters in books and 188 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 50 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.

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