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REVIEW ARTICLE

# Hormone Therapy and Delivery Strategies against Cardiovascular Diseases

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**Abstract:** This review article is aimed to delineate the potential role of hormones in the treatment and diagnosis of cardiovascular diseases with special emphasis on the nitric oxide (NO) involved mechanisms. This review will also offer an overview on current and future hormone usages, pathophysiology, clinical features, absorption mechanisms and adverse effects. The hormone therapies against cardiovascular diseases as well as their treatment strategies, delivery routes and carriers were thoroughly discussed.

Ongoing and future basic and clinical research with hormone will provide important insights into efficient treatment strategies against cardiovascular diseases. It was necessary to explore advanced delivery systems, such as drug eluting stent, microneedles, nanotechnology and stem cell preconditioning, for an efficient delivery of hormones against cardiovascular diseases. The future is enlightened with the advent of novel, safer and more effective carriers for hormone delivery as well as learning how to maximize the therapeutic efficacy against cardiovascular diseases.

**Keywords:** Hormone, delivery, cardiovascular, regulation, preconditioning, stem cell transplantation.

## 1. INTRODUCTION

Hormone is a type of chemical signal that acts as chemical messengers and regulators to induce specific adjustment in the cellular activity of target cells and maintain physiological homeostasis. Each hormone is unique in its functions that involve immunity, metabolism, growth, mood swings, reproduction, hunger and even apoptosis [1]. Hormones are functionally interconnected from brain to pituitary to adrenals to gonads, so any therapeutic intervention will alter the endocrine regulation with both beneficial and adverse activities.

Hormones are produced and secreted by cells or glands in response to the changes in the physiological balance of the body and circulated via the blood stream. The hormonal levels decrease with age and sex specifically influence personality, behavior and health of males and females. In target tissues, hormones act through specific receptors whose interaction may be based on either membrane, cytoplasmic or nuclear.

The cardiovascular homeostasis plays a pivotal role in regulating vital body organs and their functions, and any damages or constriction to cardiovascular vessels can be fatal with no prior symptoms. Because hormones have major impact on blood composition, energy levels, bone loss, sleep, body weight, metabolism, immunity, mental and physical health, hormones can be used as both diagnostic and treatment agents against cardiovascular diseases [2]. Cardiovascular hormones are either produced and secreted by cardiomyocytes or produced elsewhere and delivered to the site of action [3, 4]. Upon secretion, they bind to specific receptors in cells, activating the signal transduction mechanisms in the target organ and regulating its activity. Even though abnormal hormonal level is indicative of fatal cardiovascular diseases. Hormone therapy is most often used as an adjuvant therapy to help reduce the risk of the cardiovascular diseases [5].

The major challenge in cardiovascular therapy includes identifying and designing of efficient carriers for hormone delivery, which help to reduce the rate of morbidity and mortality from cardiovascular diseases. Current guidelines indicate that, as with all medication, hormones and their routes/carriers for cardiovascular therapy should be selected and initiated by weighing benefits and risks for the individual patient. Moreover, the long-term follow-up of clinical outcomes including prior hormone usages, and subgroup information on cardiovascular genetic disorders, is necessary to address the integral issue in hormone therapy against cardiovascular diseases [6].

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Nitric Oxide (NO) is a diatomic signaling molecule which, after production in tissues, may act as an endocrine molecule [7]. NO is a well-known marker, anti-platelet agent, vasodilator and local cell growth regulator [8]. NO covalently binds to the sulfhydryl group of cardio protective protein to form s-nitrosothiol group, hence transforming the protein into its cardio-protective status. Nonetheless, NO is highly reactive, and diffuses spontaneously across the cell membranes [9]. NO is known to regulate hormone mediated vital cellular responses in cardiovascular systems. Patients having the low levels of growth hormone are subjected to high risk of death from cardiovascular disease, and recombinant growth hormone therapy recovered NO production to the normal level [10]. Thus, it is integral to investigate the endocrine role of NO and/or its metabolites (i.e. nitrite and nitrate) in hormone regulation involved with cardiovascular diseases.

The primary goal of this review is to identify the potential role of hormones in the treatment and diagnosis of cardiovascular diseases with special emphasis on the NO-involved mechanisms. The hormone therapies against cardiovascular diseases as well as their delivery routes and carriers, as depicted in Fig. (**1**), were thoroughly reviewed.

## 2. HORMONE REGULATION AND CARDIOVASCULAR DISEASES

### 2.1. Symptoms of Hormone Imbalance

There are numerous medical and physiological triggers for hormone imbalance including birth control pills, stress, cosmetic over-usages, obesity, tumors, pregnancy, auto-antibody production and lack of exercise [11]. Most of these causes are stemmed from enhanced estrogen or estrogen dominance in the body and the low amount of progesterone. Although the symptoms of hormone imbalance are gender specific, the most commonly shared symptoms of hormone imbalance include fatigue, mood swings, weight problems, diminished sex drive, skin problems or acne, and loss of memory [12]. These symptoms become more critical with age into abnormal heartbeat, arthritis, chronic fatigue syndrome, fibromyalgia, anxiety attacks, enhanced dryness in the mouth, eyes and genitalia, and urinary tract infections [13, 14].

Hormone imbalance is typically treated with drugs or synthetic hormones, intended to resemble different segments of hormone pathways and alleviate pathological conditions [15]. The initiation time of hormone therapy in relation to

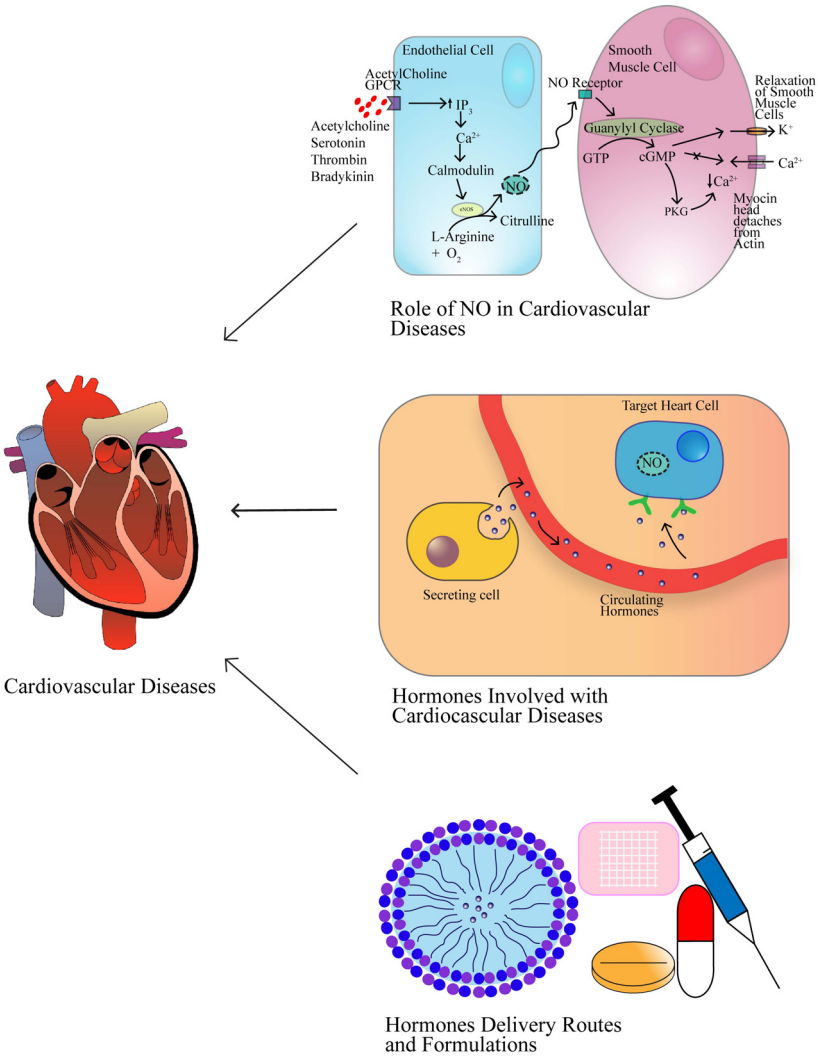


**Fig. (1).** Schematic overview of the review study.

proximity to menopause has been identified as a potentially integral predictor of cardiovascular disease outcomes in women [16]. A finding of the efficient routes and carriers for the delivery of those mimicking compounds is integral to achieve the maximum efficacy of hormone therapy.

### 2.2. Heart and Cardiovascular Diseases

The differences in vascular responsiveness and disease onset are likely related to hormone regulation that differs between men and women. Hormones involved with the cardiovascular functions are also associated with endothelial dysfunction [17], and thus most cardiovascular diseases are greatly influenced by impaired NO pathways/production (Table **1**) [18-32], [33, 34].

#### *2.2.1. Coronary Angina*

Patients with coronary angina exhibit endothelial dysfunction in spasm arteries. The major cause for the development of atherosclerosis is oxidative stress and endothelial dysfunction [35, 36]. Protective role of NO against coronary angina is elicited via inhibition of intracellular adhesion molecule 1 (ICAM-1) and enhancement of matrix metalopeptidase-13 (MMP-13) expression [37]. NO also induces vascular smooth muscle cell (VSMC) apoptosis through Fas (a death signaling molecule), but the impact of VSMC apoptosis on the onset and progress of atherosclerosis is not yet fully elucidated [38].

#### *2.2.2. Hypercholesterolemia*

Hypercholesterolemia is associated with abnormal endothelial dysfunction, enhanced NO breakdown from oxidative stress, superoxide anion production and overexpression of dysfunctional vascular soluble guanylyl cyclase [39]. Cholesterol regulates inducible isoform of NO synthases (iNOS) expression and escalates oxidative-stress induced cardiovascular tissue injury [40]. A treatment with lipid lowering drugs and endothelin receptor antagonists enhances NOS activity in hypercholesterolemia patients [41]. NO, in turn, phosphorylates ATP-sensitive K+ channels via NO cGMP-protein kinase G (PKG) (or NO-cGMP-PKG) pathway in ventricular myocytes, protecting patients from hypercholesterolemia induced microvascular injury [42, 43].

#### *2.2.3. Hypertension*

An inhibition of NOS and endogenous NO production causes elevated vascular resistance and high blood pressure. NOS inhibitors trigger hypertension by elimination of NO neural function, but has no effects on the release of endothelial NO. A majority of the treatment options against hypertension, such as calcium antagonists and hormonal therapies, act on restoring NO availability [44, 45]. Inhaled NO was efficient in reducing pulmonary arterial pressure in hypertensive children. However, the role of NO in the regulation of blood pressure varies from children (high) to adults (low) due to varying activities of NOS in different age groups [46].

#### *2.2.4. Congestive Heart Failure (CHF)*

Oxygen deprivation or hypoxia is a critical pathological condition, often leading to fatal complications. NO molecules are diffused into red blood cells in response to the hypoxic conditions, promoting NO bioavailability [47]. Levels of NO bound to hemoglobin are inversely proportional to the volume of cardiac output and act as a marker in congestive heart failure (CHF) [48]. Apart from NO production and activity, iNOS, one of the three isoforms of NOS, is over-expressed in endothelial and myocardial cells, which is mainly caused by either dilated cardiomyopathy or ischemic heart disease of the CHF patients [49]. NO exerts vasorelaxation along with endothelial NOS (eNOS) activation, which is the key target for CHF treatment [22-24].

#### *2.2.5. Carotid Artery (Supply Blood to the Brain) Disease*

The causative mechanism in carotid artery (i.e., a blood supply to the brain) disease is similar to that of the coronary artery disease. A long-term inhibition of endothelial NO synthesis leads to thrombogenicity through angiotensin-II [50]. NO along with prostaglandins inhibits endogenous growth of intimal thickening in carotid arteries [40]. In shear stress conditions, NO production is stimulated as part of body homeostasis mechanism, which protects the carotid arteries from the Progression of vasoconstriction [51]. At the same time, an excess amount of NO yields cardiogenic shocks, promoting the production of reactive oxygen species (ROS). Thus, eNOS induced NO release has protective effects, whereas the iNOS simulative process has harmful effects on the progress of vasoconstriction [52].

#### *2.2.6. Myocardial Infarction*

The pathological symptoms of myocardial infarction include eNOS deficiency that results in an imbalance between NO production and oxidative stress [53, 54], which was reversed by the enhanced expression of eNOS as well as stimulation of pathway involved with serine/threonine kinase/protein kinase B (Akt/PKB) [55, 56].

#### *2.2.7. Acute and Hypersensitive Stroke*

The high level of NO is detected in the serum of acute stroke patients [57]. NOS substrates protect elder people from being attacked by stroke through improving cerebral blood flow and cyclic adenosine monophosphate (c-AMP) levels. The chronic estrogen treatment provides stroke patients with neuro-protective effects via phosphoinositide 3-kinase (PI3K)-Akt pathway and over-regulating eNOS protein expression, that stimulates non-nuclear glucocorticoid receptors [58, 59].

## 3. HORMONES INVOLVED WITH CARDIOVASCULAR DISEASES

Hormones are chemical messengers of the human endocrine systems that travel through bloodstream to target tissues. The Endocrine system controls the functions of the body by secreting various hormones into the blood that bind to the receptors on or within the target cells to initiate a specific cellular response through membrane, cytoplasmic or nuclear. Hormones and hormonal regulation is hardwired into the human genome that maintains not just the cardiovascular systems, but also immune system, growth, metabolism,

**Table 1. Cardiovascular diseases and NO involved mechanisms.**

| Cardiovascular Disease | Nitric Oxide Involved Pathogenesis | Nitric Oxide Based Benefits | 1. Medications and 2. Surgical Procedures | Ref. |
|---|---|---|---|---|
| **Angina Pectoris** | Decrease in endothelial NO production | Smooth Muscle relaxation through NO-cGMP pathway | 1. Nitrates, Beta blockers, Calcium channel blockers, Angiotensin Converting Enzyme (ACE) Inhibitors, anticoagulants, antiplatelet drugs;<br>2. Balloon Angioplasty or Coronary artery bypass (CABG), Stent implantation | [18] |
| **Arrhythmias** | | Modulation of gap junctions | 1. Beta blockers, calcium channel blockers, anticoagulants, digoxin;<br>2. Pacemakers, Cardioversion, implantable cardioverter defibrillator, catheter ablation, Maze surgery, CABG | [19] |
| **Atherosclerosis** | Reduced NO production and activity | Vasodilation, antiplatelet aggregation and inhibition of ICAM-1 & MMP-13 expression | 1. Anticoagulant drugs, Vasodilator drugs;<br>2. Balloon angioplasty, CABG, Carotid endarterectomy | [20] |
| **Cardiomyopathy** | Abnormal increase in eNOS and NO levels as local host response | | 1. Vasodilators, digitalis, ACE inhibitors, anticoagulants, diuretics, Angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers;<br>2. Heart transplant, open-heart surgery, pacemaker, left ventricular assist device (LVAD) implantable cardioverter defibrillator (ICD) | [21] |
| **Congestive Heart Failure** | NO binds to RBC acting as disease marker | Imparts vasorelaxation | 1. Diuretics, ACE inhibitors, Aldosterone antagonists, Angiotensin receptor blockers, Beta blockers, Dilatrate, Digoxin;<br>2. ICD, Biventricular Pacemakers, heart transplant | [22-24] |
| **Coronary Artery Disease** | Impaired NO production | Vasorelaxation and cardio protective effect, suppression of intimal thickening and endogenous growth | 1. Beta-blockers, nitrates and calcium-channel blockers, diuretic, ACE inhibitors, ARBs, vasodilators<br>2. CABG, coronary angioplasty | [25, 26] |
| **Myocardial Infarction** | eNOS deficiency, NO imbalance | Cardio protective and regulatory effects | 1. Thrombolytic Medicines, beta Blockers, ACE Inhibitors, anticoagulants, platelet-inhibiting drugs;<br>2. Angioplasty, CABG | [27, 28] |
| **Hypertension** | Lower NOS and NO activity | Reduces pulmonary arterial pressure | 1. Diuretics, Beta-blockers, ACE inhibitors, Calcium-channel, Vasodilators, Nervous System Inhibitors, Alpha Blockers, Alpha-Beta Blockers;<br>2. ARBs | [29] |
| **Hypercholestero-lemia** | Decrease in endothelial NO production and enhanced NO breakdown | Protects against microvascular inflammation and endothelial dysfunction | 1. Statins, ezetimibe, bile-acid sequestrants, nicotinic acid, fibrates | [30] |
| **Stroke** | High serum NO | Neuroprotection | 1. Tissue plasminogen activator, antihypertensives, platelet-inhibiting drugs, anticoagulant;<br>2. Carotid endarterectomy | [31, 32] |

bone physiology, brain function and secondary sexual characteristics. This complex interlink of hormones is primarily integrated by hypothalamus via pituitary gland, to regulate thyroid, adrenal and gonadal functions. Hypothalamus releases its own hormones to directly monitor pituitary gland, on the other hand thyroid, adrenal and gonads regulates hypothalamus and pituitary gland through negative feedback mechanism [60]. Therefore, any therapeutic interventions to this loop altering the endocrine circuitry, has both advantages and disadvantages.

Hormones in the body are structurally classified into amino acids, peptides and steroids. Lipid-soluble hormones, such as the thyroid gland hormones and steroid hormones, activate target cells by diffusion through the cell membranes, whereas the water-soluble hormones, such as most amino acid hormones, polypeptide and protein, interact with a receptor protein present on the cell plasma membrane [61]. As shown in Table **2** [62-95], the major organ specific hormones involved with cardiovascular homeostasis and diseases are described in detail. Some of the hormones that are beyond the scope of this chapter are not discussed.

### 3.1. Amino Acid Hormones

Epinephrine and norepinephrine synthesized in the medulla and thyroid hormones synthesized in the thyroid glands are the main amino acid derived amine hormones. These

**Table 2. Effects of hormones on Cardiovascular Regulations.**

| Hormones | Functions/Cardiovascular Effects | Mode of Action | References |
|---|---|---|---|
| **Thyroid Hormone** | Regulates cardiac electrophysiology, calcium currents, systemic arterial blood pressure and vasodilation | (1) Form hormone receptor complex inside nuclear to interact with target DNA sequence; (2) Enhanced levels of thyroid hormones, stimulate β-adrenoreceptors activity via cGMP to enhance NO levels | [62-65] |
| **T4** | Induces cardiac hypertrophy by stimulating RNA and protein synthesis | (1) Act via AKT signaling pathway along with phosphorylation of mTOR and eNOS; (2) In acute hyperthyroidism an imbalance in NO homeostasis causes fluctuations in blood pressure, mediated through adrenergic and muscarinic receptors; (3) Promotes NO production by stimulating nNOS, iNOS and eNOS expressions in VSMC | [66-69] |
| **T3** | Vasodilatory effect on VSMCs | | [67-70] |
| **Insulin** | Glucose homeostasis; Protective cardiovascular effects in myocardial ischemic reperfused (I/R) injury, by inhibiting polymorphonuclear leukocytes (PMNs) adherence and infiltration into to the endothelium | (1) Reduces activities of several cardiovascular pathogenesis (P47, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), ICAM-1, plasminogen activation inhibitor 1 and monocyte chemo attractant protein 1); (2) Insulin-resistance depletes NO levels altering vascular functions leading to hypertension; (3) Severe hypoglycemia provokes acute vascular events like myocardial ischemia, cardiac arrhythmia and in some cases death | [71, 72] |
| **Estrogen** | Cardioprotective effect in premenopausal women | (1) Bind to estrogen receptors (ER) (i.e. ER-α and ER-β) lowering LDL levels, superoxide generation and NO regulation in atherosclerosis patients; (2) Increases the expression of eNOS via PI3K-Akt-p-eNOS pathway and also by translocating it from plasma to intracellular sites; (3) In myocardial infarction, estrogen in endothelial progenitor cells improves the ischemic tissue condition through eNOS mediated matrix mettaloproteinase-9 (MMP-9) activation | [73-78] |
| **Progesterone** | Cardioprotective effect in premenopausal women | (1) Induces endothelial vasodilation through transcriptional and non-transcriptional pathways; (2) Promotes eNOS activation and inhibits VSMC proliferation through MAPK pathway | [79-81] |
| **Testosterone** | Cardio protective effect in men; regulates the VSMCs potassium channels, inducing endothelial independent relaxation in coronary arteries, and has beneficial effects on angina symptoms and myocardial ischemia | (1) Alters vascular function by augmenting the production of pro-inflammatory cytokines and arterial wall thickness; (2) Binds to androgen receptors or membrane receptors in endothelial and VSMCs to induce genomic and non-genomic effects respectively; (3) Maintains endothelial function by regulating the synthesis and bioavailability of NO; (4) Vascular protective properties through non-genomic systemic vasodilatory actions to enhance NO production | [82] |
| **Vasopressin** | Water retention and vasoconstriction; Increases peripheral vascular resistance | (1) Binds to V1 receptors on VSMCs to cause vasoconstriction via IP3 signal transduction pathway and Rho-kinase pathway; (2) Enhances NO production through promoting iNOS gene expression in NF-κB pathway; (3) Imbalance between profibrolic activity of arginine vasopressin and NO production is reported to trigger the onset of myocardial fibrosis | [83] |
| **Oxytocin** | Birth contractions: Regulates vascular tone, heart rate and blood pressure mediated through inducing components, such as NO, α-adrenoreceptors and atrial natriuretic peptide | (1) Regulates cardiovascular functions via activation of the cardiac receptors and stimulation of the central nervous system; (2) Exerts vasodilatory and anti-arrhythmic activities via calcium immobilization, leading to enhanced endothelial NO production; (3) Stimulates AKT expression and phosphorylation of eNOS through PI3K/AKT pathway during the cardiomyocytes differentiation | [84-86] |
| **Prolactin** | Lactation; Prolactin activities are similar to the vasodilatory effects of oxytocin | (1) Causes vasoconstriction through the beta2-adrenergic and nitric oxide involved mechanisms; (2) Inhibits IL-1β induced iNOS expression and NO production in vascular endothelial cells, lowering intracellular calcium mediated eNOS activation and anti-angiogenic properties | [87-89] |
| **Follicle stimulating hormone** | In post-menopausal women, FSH exerts protective effects against progression of CAD | In the granulose cells, FSH stimulates eNOS mRNA expression and the synthesis of BH4 that is a cofactor for NOS catalytic activity | [90, 91] |
| **Adrenal Hormones** | Responses to stress by increasing heart rate, blood pressure and oxygen supply to the brain | (1) Norepinephrine (NE) regulates NO mediated inotropic functions and enhances IL-1beta-induced NO production through MAPK pathway in cardiovascular muscles; (2) Cortisol induces hypertension by suppression of NOS pathways, especially L-arginine availability; (3) Treatment with cortisol alleviates cholinergic dilation triggered by abnormal endothelial NO levels | [92-95] |

hormones are water-soluble and act via secondary messengers on the surface of target cells. Thyroid hormones and catecholamines are derived from amino acid tyrosine, serotonin and melatonin from tryptophan and histamine from glutamic acid. Thyroid hormones and catecholamines are discussed in the below sections.

Thyroid hormones impact structural, electrophysiological and calcium mediated remodeling of vascular membrane through direct action on VSMCs [96]. Under precarious heart conditions thyroid hormone plays cardio-protective role. For instance, in stress cardiomyopathy thyroid hormones regulate myocardial contractility [62, 97]. Even in hyperthyroidism, elevated levels of thyroid hormone stimulate β-adrenoreceptors via cGMP pathway [63]. Consequently, enhanced levels of NO lower vascular resistance and prevent atrial arrhythmias by reducing potential repolarization process and effective refractory period [98, 99]. An enhanced NO production alleviates vascular tone through renal sodium excretion, maintaining homeostasis and counterbalancing the adverse effects [100, 101].

Between two types of thyroid hormones, T4 (3,5,3',5'-Tetraiodothyronine) is the major hormone secreted by the thyroid gland and follicular cells, whereas T3 (Triiodothyronine) is produced by deiodination of T4 by two deiodinase enzymes [66]. Both T4 and T3 are known to regulate cardiovascular systems via NO involved pathways [67]. The cardiovascular effects of T4 involve AKT signaling pathway along with phosphorylation of mTOR and eNOS [66]. T4 also induces cardiac hypertrophy by stimulating RNA and protein synthesis [66]. T3 promotes NO production by stimulating neuronal NOS (nNOS), iNOS and eNOS expressions in VSMC, leading to enhanced binding to the thyroid hormone receptors on endothelial cells [70].

Adrenal medulla upon responding to stress releases the flight hormones (epinephrine and norepinephrine (NE)) that increase blood pressure, heart rate and oxygen supply to the brain. In cardiovascular muscles, NE regulates NO mediated inotropic functions and enhances IL-1beta-induced NO production through MAPK pathway [102]. However, the prolonged exposure of NE exerts no activities on the L-arginine-NO production process, rather producing congestive heart failure in endothelial cells [92].

### 3.2. Peptide Hormones

Peptide or protein hormones are amino acid derived hormones with the peptide chain ranging from three to several hundred amino acids. Typically, hormones with hundreds of amino acids are known as proteins, like insulin secreted from pancreas and growth hormone secreted from anterior pituitary glands, and that with short amino acid chains are known as peptides like antidiuretic hormone and oxytocin. Hypothalamus, pituitary glands, adrenal glands, ovaries, pancreas and adipose tissue secrete peptide hormones. Non-endocrine tissues like heart tissue and gastrointestinal tissues can also secrete peptide hormones. Peptide hormones composed of carbohydrate side chain, are referred to as glycoproteins, like luteinizing hormone and follicle-stimulating hormone secreted by the anterior pituitary. Anterior pituitary glands also secrete long chain peptide molecule prolactin, and posterior pituitary glands secrete small peptide hormones like vasopressin and oxytocin.

Insulin is known as a peptide hormone consisted of 51 amino acids. There is a connective peptide named C-peptide which binds A and B chain in proinsulin that is co-secreted along with insulin when proinsulin degrades. This induces endothelial NO release and significantly reduces endothelium leukocyte interaction [103]. Insulin defends myocardial ischemic reperfused (I/R) injury, by inhibiting polymorphonuclear leukocytes (PMNs) adherence and infiltration into cardiac endothelial cells [71]. Insulin regulates the activities of several cardiovascular pathogenesis, and cardiovascular risk markers through endothelial NO synthesis [71]. Some cardiovascular risk factors like free fatty acids act through impairing insulin-mediated vasodilation and NO production [104]. An intensive insulin therapy or glucose-insulin-potassium (GIK) treatment for diabetes patients leads to NO up-regulation through AKT phosphorylation of eNOS in a PI3K dependent mechanism [105, 106], subsequently yielding cardiovascular protection [107].

Vasopressin, an antidiuretic hormone, is a potent vasopressor. In normal healthy adults, vasopressin increases peripheral vascular resistance, enhancing arterial blood pressure, forearm vasodilation and digital vasoconstriction. Vasopressin enhances NO production through promoting iNOS gene expression in nuclear factor- kappaB (NF-κB) pathway [83], alleviate coronary vasoconstriction. Based on this unique combination of properties, vasopressin is used as a cardio-protector in severe septic shock, ischemia and refractory heart failure [108-110]. A short-term infusion of vasopressin as a cardio-protector (i.e., restoring blood pressure) for severe septic shock improved renal functions [109]. Vasopressin reperfusion for the treatment of ischemia alleviates coronary vasoconstriction by reducing NO and prostanoid performance [108]. A combination of iNOS and vasopressin has beneficial effects on refractory heart failure, producing systemic vasoconstriction and low heart afterload [110].

Oxytocin mediates NO dependent cardiovascular functions via activation of oxytocin receptors, α-adrenoreceptors and atrial natriuretic peptide in the heart [84]. It is also involved in maintaining cardiovascular homeostasis through various NO related mechanisms like phosphorylation of eNOS through PI3K/AKT pathways [85]. Synthetic oxytocin like Syntocin exerts vasodilatory and anti-arrhythmic activities via calcium immobilization, leading to enhanced endothelial NO production. Similar to oxytocin, prolactin causes vasoconstriction through the beta2-adrenergic and NO involved mechanisms [87]. The N-terminal 16kDa fragment of prolactin inhibits iNOS expression in vascular endothelial cells [88], lowering intracellular calcium mediated eNOS activation and anti-angiogenic properties [89].

The role of follicle stimulating hormone (FSH) in the regulation of the cardiovascular system is not yet fully elucidated. In post-menopausal women, FSH was reported to exert protective effects against progression of coronary artery disease [90]. In the granulose cells, FSH stimulates eNOS mRNA expression and the synthesis of BH4, which is a co-factor for NOS catalytic activity [91].

The anterior lobe releases such hormones as Adrenocorticotropic hormone (ACTH), Growth hormone (GH), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Thyroid-stimulating hormone (TSH) [61]. The pituitary gland through interacting with the hypothalamus guarantees that all body organs properly function and give a signal to the anterior lobe whether to produce more of a specific hormone or stop its release [111].

### 3.3. Steroid Hormones

Steroid hormones are cholesterol-derived hormones that are grouped into two classes namely corticosteroids and sex steroids. The *adrenal* cortex mainly produces five classes of steroid hormones: glucocorticoids, mineralocorticoids, estrogens, progesterone, and androgens.

Estrogen has been long known to impart cardio-protection in premenopausal women [112]. Estrogen treatment to patients with impaired vascular performances and atherosclerosis reduces norepinephrine-induced vasoconstriction and promotes endothelin-mediated vasodilation. However, estrogen treatment sometimes worsened the symptoms of coronary atherosclerosis and angina pectoris in diabetic postmenopausal women [113]. Although highly debated to this day, estrogen therapy in combination with progesterone for healthy postmenopausal women can alleviate stroke risk [114, 115] and coronary heart disease [116].

Cortisol is an essential glucocorticoid that regulates and supports several vital functions of the body. In humans, cortisol induces hypertension by suppressing NOS pathways, especially L-arginine availability [93]. The treatment of cortisol alleviates cholinergic dilation triggered by abnormal endothelial NO levels [94].

Aldosterone is the main mineralocorticoid hormone produced by the adrenal cortex present in the adrenal gland [117, 118]. Aldosterone binds to and activates the mineralocorticoid receptor in a plethora of tissues, and regulates blood pressure mainly by increasing reabsorption of ions (retain sodium and release potassium) and increasing water retention in the kidney [119, 120]. Aldosterone in a dysregulated form contributes to the development and progression of cardiovascular and renal disease [15, 121]. Aldosterone is now considered as an essential treatment option against heart failure owing to the opposite function of the atrial natriuretic hormone, which is secreted by the heart and has important natriuretic and kaliuretic properties [122].

### 3.4. Nitric Oxide

Nitric oxide acts as a neurotransmitter and intracellular messenger to regulate cardiac rhythmicity, growth and contractile performance, by receiving and executing the instructions from endocrine systems. Although not fully understood, the wide variety of roles and functions of NO, support NO as a hormone. Hence understanding the molecular mechanism of NO in cardiovascular cells is imperative to this review.

Endothelium and endothelial gap junctions are vital to cardiovascular homeostasis and NO regulate their function at cellular level. Endothelial dysfunction is characterized by impaired NO production and low availability in endothelial cells [123]. A decrease in NO production by reactive oxygen species (ROS) generally yields deleterious effects on the vascular system [124]. NO donors stimulate the formation of gap junctions and modulates gap junction coupling in vein endothelial cells through protein kinase A (PKA) activation pathway [19, 125]. Nitrates increase NO bioavailability and guanylyl cyclases mediated conversion of Guanosine-5'-trihosphate to cGMP [126]. Enhanced cGMP via PKG), inactivates myosin light chain kinase, reduces calcium influx and dephosphorylates myosin light chain, Myocin-LC-Po4 to Myocin-LC, causing smooth muscle cells relaxation [127, 128]. Although NO in itself is not a hormone it exerts a direct effect on the secretion of the pituitary hormones, gonadotropins and adrenocorticotropic hormone (ACTH), and at the same time suppresses the release of prolactin (PRL) from pituitary glands and that it is directly involved in the control of growth hormone (GH) secretion. However, whether NO dependent cGMP pathway mediates these hormonal effects, stimulatory or inhibitory, is yet to be fully understood.

## 4. DELIVERY ROUTES FOR CARDIOVASCULAR HORMONE SYSTEMS

The hormone delivery system for the cardiovascular therapy has been defined based on (a) sites of action, (b) sustained/controlled action, (c) application to disease, and (d) routes of delivery [129]. As shown in Fig. (**2**), currently available and potential routes and techniques for the hormonal formulations against cardiovascular diseases have been reviewed in this section.

Although gigantic progress has been made in the past decades, most hormone delivery systems currently available encounter severe shortcoming of being incomplete methodology and limited routes for administration (Table **3**) [116, 130-163]. The oral route was reported to be associated with a lower risk of stroke, whereas transdermal route seemed to be linked to a lower risk of coronary heart disease as compared with conventional oral regimen. It was also suggested that transdermal route may have advantages in minimizing the risk of cardiovascular disease onset associated with hormone therapy.

### 4.1. Oral Route

Despite numerous advances in the drug delivery systems in the past few decades, the oral route is the most favorable choice from all the age groups and has access to the largest market. The absorption of loaded hormones from the oral formulations, such as tablets, capsules and drops, is mainly governed by drug permeation across the epithelial cell membrane in the gastrointestinal tract. The oral delivery of hormones needs to be taken with special dietary regulations, because food tends to slow gastric emptying and influences their absorption rates. Nonetheless oral route is also associated with a lower risk of stroke as compared with other routes including transdermal route [164].

#### *4.1.1. Tablets*

Most hormonal tablets available in the market are for steroid hormones, such as estrogen, progesterone, testosterone and their combinations for contraceptive pills or hormone disease therapy; all of them were explored for their potential cardiovascular risks. 17β-estradiol showed enhanced cardiac hypertrophy, whereas estradiol valerate showed no associated risks [165, 166]. It is also reported that the use of combined postmenopausal hormone therapy, such as estrogen-plus-progestin, lowered the incidence of coronary heart disease among women using these medications [167]. Besides steroid hormones, levothyroxine is another hormone marketed as tablets for the treatment of hypothyroidism in elderly people [168].

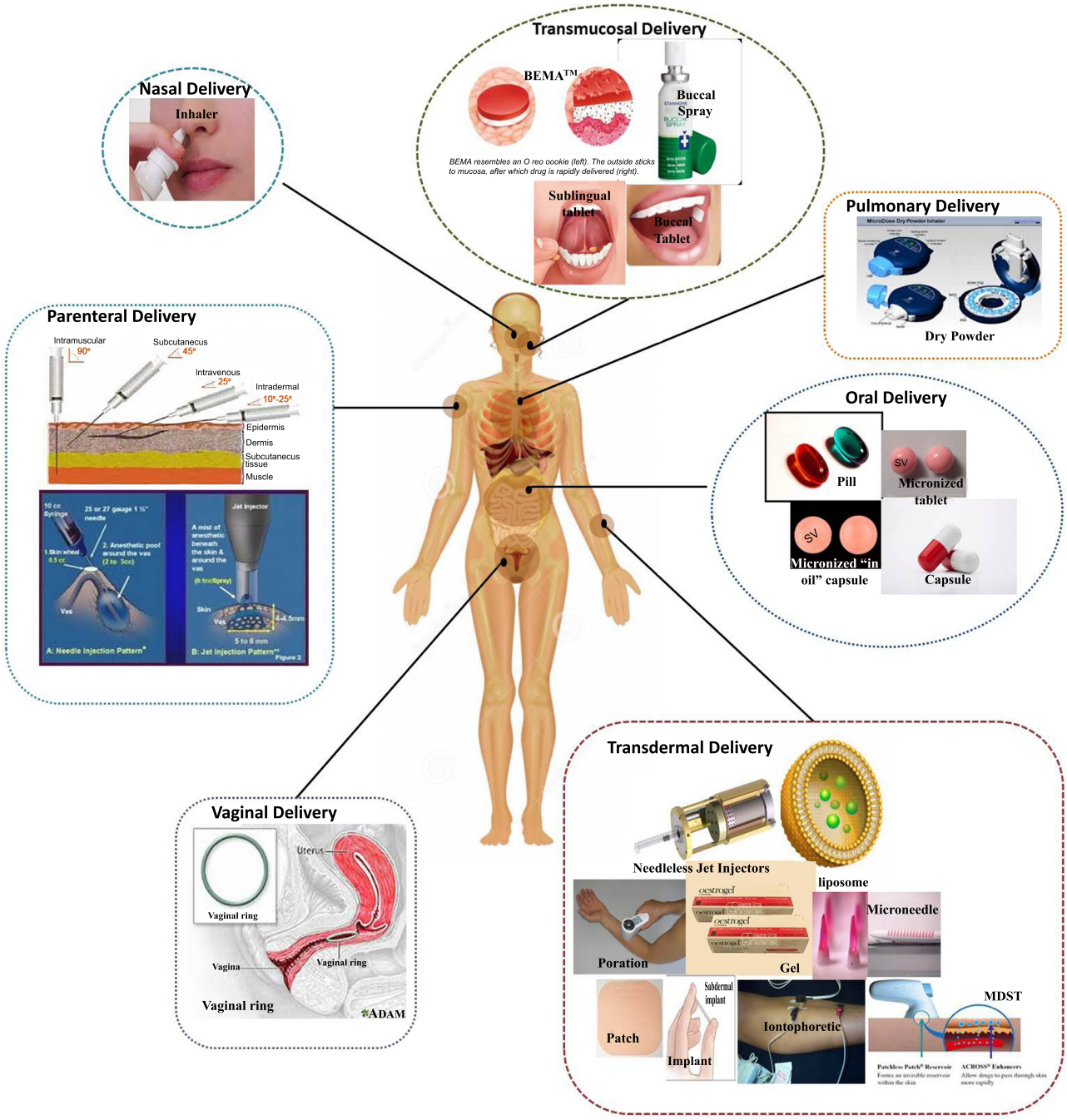


**Fig. (2).** Drug delivery of hormone for cardiovascular disease.

### *4.1.2. Micronized Drug*

The micronized particle for delivery of drug has been introduced to solve the dissolution and bioavailability challenges. Most hormones are poorly water-soluble which causes the dissolution and bioavailability issues. The dissolution rate can be improved *via* micronization process of specific hormones.

#### *4.1.2.1. Oral Micronized Hormone Tablets*

Oral micronized progesterone tablet in combination with transdermal estradiol has been used as the preventive strategy against menopause symptoms. This strategy has achieved substantial decline in the number of risk factors for cardiovascular disease onset and progress by reducing the accumulation of coronary calcium and ceratoid intimal medial thickness [131]. It is also reported that micronized progesterone and pregrane derivatives are safe from the thrombotic risk [169].

#### *4.1.2.2. Micronized Hormone 'in oil' Oral Capsule*

For improved absorption, formulation of micronized "in oil" seemed to be more effective than micronized tablet. It showed that micronized progesterone USP in peanut oil vehicle (Prometrium®) are readily absorbable in the blood

stream and achieve enhanced progesterone blood serum levels [170].

**Table 3. Delivery systems for hormones.**

| Delivery Systems | Target Hormones | References |
|---|---|---|
| **Oral** | | |
| Tablets | Estrogen, progesterone, testosterone, levothyroxine | [116, 130] |
| Micronized | Estrogen, progesterone, HRT | [131] |
| Capsules | Insulin, cortisol, melatonin, dehydroepiandrosterone | [132-134] |
| **Transmucosal** | | |
| Sublingual | Estrogen | [135] |
| Buccal Tablets | Testosterone | [136, 137] |
| Buccal Spray | Insulin | [138-140] |
| **Transdermal** | | |
| Gels | Testosterone, estrogen, progesterone | [141] |
| Patches | Estrogen | [142] |
| Subcutaneous Implants | Estrogen, progesterone, insulin, thyroid hormone | [143, 144] |
| Iontophoretic Delivery | LHRH, Calcitonin | [145] |
| MDST | Estradiol | [146] |
| Needleless Jet Injectors | Insulin | [147, 148] |
| Microneedles | Parathyroid hormone, hGH | [149-151] |
| **Nasal** | | |
| Intranasal | Estrogen | [152] |
| Inhalation | Oxytocin, hGH | [119, 153, 154] |
| **Pulmonary** | | |
| Pulmonary | Insulin, calcitonin, hGH, TSH, FSH, somatostatin, vasopressin | [155-157] |
| **Parenteral** | | |
| Subcutaneous | Growth hormone, insulin | [158] |
| Intravenous | Estrogen | [159] |
| Intra-arterial | Corticotrophin releasing hormone | [160] |
| Intrathecal | Estrogen | [161] |
| Intramuscular | Testosterone, estrogen, progesterone | [160] |
| Intraperitoneal | Thyroid hormone, growth hormone | [162, 163] |
| **Vaginal** | | |
| Vaginal rings | Estrogen, HRT | [163] |

#### *4.1.3. Capsules*

Hormones have been vastly studied in capsules, but a few hormones like insulin, cortisol, melatonin, and dehydroepiandrosterone, were formulated in a form of the capsules, whose therapeutic potential in cardiovascular application is yet to be validated [132-134].

### 4.2. Transmucosal Route

Drug delivery through mucous membrane is one of the most effective routes for hormones against heart diseases. The highly vascularized mucosa bypassed the first-pass metabolism occurred in the liver, thus achieving rapid onset of pharmacological action equivalent to the intravenous route [171].

#### *4.2.1. Mucoadhesive Sublingual Tablet*

Estrogen therapy in post-menopausal women administered sublingually exerted some beneficial effects, such as endothelium dependent vasodilation and the reduced release of endothelin-1 [135, 172, 173].

#### *4.2.2. Mucoadhesive Buccal Tablets*

Within the oral mucosa cavity, the buccal region between the cheek and gum offers an attractive route of administration for systemic drug delivery. Testosterone in buccal tablets enhances cardiac output and imparts other therapeutic benefits in men with chronic heart failure [136, 137]. Among all the NO donor families, Nitrates are especially formulated into buccal tablets for the treatment of angina and heart attack.

#### *4.2.3. Buccal Spray*

An aerosol spray delivers the drug at the constant dose in fine particulates or droplets onto the mucosal surface or into the salivary fluid [138]. Insulin has been a popular candidate for the spray formulations [139, 140]

### 4.3. Transdermal Route

Due to a variety of advantages over other delivery routes and high patient compliance, transdermal systems serve as an efficient alternative for oral formulations [141]. The transdermal route may have advantages of reducing the adverse effects associated with long-term oral hormonal therapy and minimizing the risk of cardiovascular disease onset associated with hormone therapy [164].

#### *4.3.1. Gels*

Transdermal gel containing a combination of progesterone and estrogen gel demonstrated beneficial effects on myocardial ischemia in postmenopausal women. Transdermally delivered estrogen also reduced the plasma level of fibrinogen and factor VII, which are known important risk factors for cardiovascular disease [174]. Transdermal gels for dihydrotestosterone are effective in reducing side effects and safer than other androgen replacement therapies from the perspective of atherogenicity. Testosterone gels were also effective in reducing body fat and alleviating sexual dysfunction in both men and women [175, 176].

#### *4.3.2. Patches*

Estrogen patches have similar low adverse effects to the transdermal gels [142]. Estrogen in a patch formulation exerts cardio-protective activities in post-menopausal women with type II diabetes [177, 178]. It is also reported that the supplemental treatment of testosterone at low-doses in a transdermal patch form reduced exercise-induced myocardial ischemia in men with chronic stable angina [179], even though the effects of patches vary with age groups [180, 181].

#### *4.3.3. Subcutaneous Implants*

Subcutaneous implants avoid first pass metabolism of the hormone and subsequently increase bioavailability, alleviating postmenopausal symptoms and cardiovascular risks [143]. Estrogen delivered through subcutaneously implantable pellets showed neuro-protective effects via ER-β binding and reduced the risk of coronary artery disease by modulating constrictor responses of atherosclerotic arteries [143, 182]. A combination of progesterone and estrogen in subcutaneously implantable pellets further attenuates coronary artery disease in postmenopausal women. Similarly, insulin subcutaneous implantation effectively prevents neointimal formation in both VSMC and endothelial cells [144].

Since implantable pellets require a surgery for implantation and/or removal, biodegradable microspheres were widely used for hormones, such as growth hormone and sex hormones [183]. Prolonged-release properties of microspheres can avoid the frequent drug-intake and improve patient compliance by maintaining the therapeutic levels in the body [184].

#### *4.3.4. Iontophoretic Delivery*

Iontophoresis used an electrical potential to drive charged drug molecules into the skin and capillaries [185]. A drug depot in the skin from iontophoretic delivery of LHRH is approximately twice as large as the total amount of drug delivered systemically. A combination of iontophoresis and electroporation reduced the lag time of iontophoretic delivery of salmon calcitonin, achieving greater transdermal permeation rate than either one technique alone [145].

#### *4.3.5. Meter Dosed Transdermal Spray (MDST)*

MDST has been used to form an invisible drug depot and deliver a drug to the skin surface. Evamist® is a MTDS product for estradiol delivery [146] that has achieved the improved plasma level [186].

#### *4.3.6. Needleless Jet Injectors*

Needleless jet injectors take advantages of parenteral and transdermal drug delivery routes. PowderJect, a best-known injector utilizing high-pressure helium gas, delivers fine, solid particles via the stratum corneum [147]. Both preclinical and clinical studies demonstrated that the needleless jet injection is much easier to handle and bioequivalent in therapeutic drug levels to conventional subcutaneous delivery [148].

#### *4.3.7. Microneedles*

Microneedle patches was developed to produce larger transport pathways via combining the transdermal patches with the merit of delivering macromolecules obtained from hypodermic needle [149, 187-190]. The administration of hGH via microneedle patches was effective without loss of functional activity [150]. The combination of microneedles and iontophoresis for the delivery of hGH was also very effective [151].

### 4.4. Nasal Route

In the intranasal delivery system, a drug is delivered across highly vascularized nasal mucosa into the blood stream [191]. The major advantages are needle-free application mode and the permeable application site in the nasal cavity that allow a rapid onset of local and systemic drug actions [192]. The nasal route is rapidly evolving as a cost effective, patient compliant delivery system for respiratory drugs and hormones against sinus allergies and lung problems [152]. Moreover, transmucosal nasal absorption prevents drug from gastrointestinal destruction and avoids hepatic first-pass metabolism.

### 4.5. Pulmonary Route

The immense capacity, large surface area, good vascularization and ultra-thinness of the alveolar epithelium are unique features of pulmonary delivery route that can expedite systemic delivery of various drugs, proteins and peptides [193]. A number of studies have investigated the pulmonary delivery of various biologics including insulin and growth hormone [154].

Inhalable polymeric nanoparticles based drug delivery system have also been studied for the treatment of tuberculosis and cardiovascular diseases [194, 195] Such approaches allow the direct delivery of insulin molecule to the bloodstream without undergoing degradation. A powder aerosol based on GRAS excipients significantly enhanced the absorption rate of hGH through the lung mucosa [155]. There is uncertainty about the effectiveness of the intranasal delivery of neuropeptides, but a recently study on inhaled vasopressin has shown similar behavioral and physiological effects to those observed with peripherally injected formulations in rats [156].

### 4.6. Parenteral Route

Although it is not the most preferred delivery system and has the risk of bypassing body's natural defense mechanism, most hormones can be delivered via parenteral routes.

#### *4.6.1. Subcutaneous*

An insulin port serves as a delivery channel for various pharmaceuticals directly into the subcutaneous compartment. The syringe needle remains above the skin surface, whereas the drug is delivered into the subcutaneous region through the soft cannula [196].

#### *4.6.2. Intravenous*

17β-estradiol administered via IV route was efficient in cardio-protection in menopausal women [158]. An intrave-

nous (IV) administration of vascular endothelial growth factor has also demonstrated its beneficial effects on cardiomyocytes performance and prevention of apoptosis [197].

#### *4.6.3. Jet Injectors*

The jet injector uses a narrow high-pressure jet of the injectable liquid rather than a hypodermic needle to enter the epidermis. The power of a jet injector comes from compressed gas or air. Insulin is the primary candidate administered through jet injecting as an alternative option against diabetes [198].

#### *4.6.4. Intramuscular*

An intramuscular (IM) administration of testosterone displayed immense beneficial effects on angina pectoris and atherosclerosis. However, there were some contradictory outcomes from the cardiovascular system after IM administration of testosterone, which needs long-term clinical observation and thorough outcome assessment [199, 200].

## 5. ADVANCED APPROACHES FOR CARDIOVASCULAR DISEASE DIAGNOSIS AND THERAPY

### 5.1. Nanotechnology for Hormone Delivery

Nanotechnology has been extensively explored in the drug delivery field owing to their unique merits, such as controlled release, drug protection, and targeted accessibility to various tissues, cells and subcellular organelles like nucleus intended for gene delivery. Numerous hormones, such as estradiol, testosterone, parathyroid hormone, growth hormone releasing factor, and recombinant hGH (rhGH), have been delivered by devices equipped with nanotechnology. Nanotechnology based delivery systems include nanoparticles, polymeric hydrogel and lipid based drug delivery systems (i.e., solid lipid nanoparticles and liposomes) [201].

#### *5.1.1. Nanoparticles*

Nanoparticles are mainly intended for administration of drugs through the parenteral route, but also applied to the mucosal sites. They have been utilized not only as a protective carrier for the drug from degradation and extending their duration in the body, but also explored as a controlled delivery system with varying release profiles and therapeutic efficacy depending on the biomaterial bases.

The nanoparticles system in which estradiol was incorporated into PLGA nanoparticles was designed to improve its oral bioavailability [202]. Besides PLGA, $Zn^{2+}$ dextran is also used as a base for rhGH-Zn2+-dextran nanoparticles which are intended for numerous delicate proteins [203]. Other well-known system of nanoparticles against cardiovascular disease is silica nanoparticles made from the synthesized N-diazeniumdiolate-modified aminoalkoxysilanes [204] and intended to deliver Nitric Oxide (NO), producing cGMP and ultimate dilatation of blood vessels [205].

#### *5.1.2. Solid Lipid Nanoparticles (SLN)*

SLN is known as a non-toxic colloidal drug carrier prepared with physiological lipid molecules applied as pharmaceutical excipients via solidified emulsion (dispersed phase) technologies. SLN usually offers a low loading yield owing to drug exclusion upon polymorphic transition during the storage process, especially when the lipid matrix is made of similar molecules [206]. Due to hydrophilic nature, surfactants worked as emulsion stabilizers for most proteins that are expected to be poorly microencapsulated into the hydrophobic matrix of SLN. SNL have been examined for stability, the release kinetics and *in vivo* efficacy of various therapeutically effective peptides, model drugs and protein antigens [184].

#### *5.1.3. Liposomes*

Liposomes are a particulate carrier system that has been frequently explored for the local site-specific drug delivery with controlled release property. Liposomes are made of phospholipid bilayers isolated by internal aqueous parts [207]. The major merit of liposomes is the biocompatibility with the body system, thereby exerting negligible inherent toxicity [208]. A liposomal carrier prepared by phosphatidylethanol was successfully and efficiently developed for oral delivery of insulin [209].

### 5.2. Cardiovascular Stent for Hormone Delivery

Stents are one of the fast-growing drug delivery systems and have been vastly researched for the treatment of heart diseases including coronary artery diseases [210]. At present, estrogen is the only hormone formulated and tested to treat CAD via hormone-eluting stents. 17β-estradiol was successfully loaded on the stent surface coating for the prevention of restenosis through revascularization, re-endothelialization and inhibition of extracellular-signal-regulated kinase [51] activation in VSMC [210, 211].

Numerous coating materials and techniques including nanofibers for hormone-eluting stents have been tested to achieve the efficient delivery of hormones against cardiovascular diseases [212]. In addition, advanced drug carriers, such as DNA-based delivery systems and integration of biosensors and drug delivery technologies, can be explored for an efficient delivery of hormones against cardiovascular diseases [213, 214].

### 5.3. Hormone Preconditioning for Stem Cell Transplantation

Targeted stem cell therapy is currently one of the most promising treatment options for acute or chronic myocardial infarction. Screening/selecting cell types and development of in vitro cell-culture methodologies to drive stem cell differentiation is crucial to the success of these therapies [215]. Among stem cells, mesenchymal stem cells, adult progenitor cells, and autologous bone marrow stem cells, are the most widely used for cardiovascular application [216]. The delivery of stem cells is performed through intracoronary cell infusion or direct intra-myocardial cell injection to the infarct site [217]. In the last decade, various enhancement strategies for stem cell therapies have been studied, and aside from growth factors, hormones are considered as a good source for stem cell proliferation, maturation, migration and homing.

Thyroid hormone, T3, plays a vital role in the overall heart maturation and development. The levels of T3 decline in response to various stresses in the human body and are responsible for fetal cardiomyocytes development and gene regulation [218]. As T3 supplemented to the cultures of induced pluripotent stem cells and embryonic stem cells (ESCs) differentiate into mature adult like cardiomyocytes, it can serve as an excellent candidate for the treatment of myocardial infarction.

Sex steroids facilitate numerous intracellular mechanisms responsible for heart homeostasis. Estrogen reduces the level of superoxide and increases anti-apoptotic, anti-inflammatory and nitric oxide mediated activity, promoting cardiovascular health in woman. More interestingly, estrogen also exerts anti-ischemic activity by stimulating endothelial progenitor cell mobilization and VEGF release from mesenchymal stem cells [219]. Estrogen via estrogen receptors triggers endothelial progenitor cells proliferation, and migrates to injured cardiac tissue [220]. Estrogen also stimulated hematopoietic stem cells, which are a heterogeneous stem cell population capable of blood, myeloid and lymphoid cells production [221]. The pretreatment/preconditioning of estrogen and testosterone in stem cells differentiate into not only cardiac phenotypes but also sexually dimorphic cells that could hold the key to gender specific stem cell therapies in the future.

Oxytocin assists proliferation of postpartum alveolar and myoepithelial cells required for milk production in mothers. Recent studies have shown that oxytocin is responsible for P19 embryonic stem cell differentiation into cardiomyocytes. Oxytocin also induces *in-situ* differentiation of cardiac progenitor cells into cardiomyocytes in the tissue regeneration and repair processes [222] through the mechanism which has been attributed to cardiac gene expression in P19 embryonic stem cells and cardiac stem cells [214]. Thus, hormone based stem cell preconditioning could serve as a synergistic method to enhance tissue specific cell differentiation, retention and homing in stem cell therapy.

### 5.4. Hormones in Cardiovascular Disease Diagnosis

Early diagnosis of cardiovascular diseases is a major clinical challenge. Most patients experience silent symptoms that are often undiagnosed until severe blockage or pain occurs. Popularly known as a major organ of the circulatory system, heart also plays a dual role of an endocrine organ. Heart synthesizes two structurally similar peptide hormones namely, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). C-type natriuretic peptide (CNP) also belongs to the family of natriuretic peptide hormones secreted from the vascular endothelial layers. Natriuretic peptide hormones bind to specific receptors, called ANP-receptors (ANP-A and ANP-B) with varying affinities to regulate ion channels and cGMP dependent PKG pathways. BNP exists as its precursor in myocytes that is released in response to pressure overload, to produce active BNP and inactive NT-proBNP (N-terminal fragment of prohormone). Although inactive, NT-proBNP is also a marker for cardiovascular risk assessment. BNP and NT-proBNP (N-terminal fragment of prohormone) have longer biological half-life compared to ANP, and thus they are better biomarkers for both disease diagnosis and prognosis [223]. Role of BNP as a biomarker for various cardiovascular diseases has been well established clinically [224]. Numerous studies are underway to combine BNP-testing with cardiovascular therapies and disease prognosis systems to develop advanced personalized treatment strategies with higher chances of survival [225].

## CONCLUSION AND FUTURE PROSPECTS

Once considered to be a last resort, hormone therapies gradually become a mainstream choice, if still not standard care option for cardiovascular diseases. The hormone therapy generally functioned as an adjuvant therapy and provides broad homeopathic remedies that reflect each person's physiological status to recover balance and alleviate hormone deficiency symptoms. Several factors including the different formulations, and initiation time and duration period of hormone therapy, seem to be associated with various side effects, especially onset of cardiovascular diseases. Studies are underway to assess outcomes that hormones delivered through various carriers at the early stage of cardiovascular diseases have offered greater therapeutic response and recovering rates.

The combinatory therapy of hormones and endogenous compounds like nitric oxide (NO) may provide important insights into efficient treatment strategies against cardiovascular diseases. The future is brightened with the advent of safer and novel carriers for hormone and NO delivery as well as learning how to maximize the therapeutic efficacy against cardiovascular diseases already at our disposal.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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## REFERENCES

[1] Mori, K. *Chemical synthesis of hormones, pheromones and other Bioregulators*, 1st ed.; Wiley & Sons: New York, vol. 314, **2010**.

[2] Bader, M. *Cardiovascular hormone systems: From molecular mechanisms to novel therapeutics*1st ed.; Wiley-Blackwell, 2008; p 456.

[3] Miller, R.D.E.; Fleisher, L.; Wiener-Kronish, J.P.; Young, W.L. Miller's Anesthesia. 7 ed.; Churchill Livingstone: **2009**; pp. 3312.

[4] Clerico, A.; Giannoni, A.; Vittorini, S.; Passino, C. Thirty years of the heart as an endocrine organ: Physiological role and clinical utility of cardiac natriuretic hormones. *Am. J. Physiol. Heart Circ. Physiol*., **2011**, *301*(1), H12-20.

[5] Ruskoaho, H. Cardiac hormones as diagnostic tools in heart failure. *Endocr. Rev.*, **2003**, *24*(3), 341-356.

[6] Shufelt, C.L.; Bairey Merz, C.N. Contraceptive hormone use and cardiovascular disease. *J. Am. Coll. Cardiol*., **2009**, *53*(3), 221-231.

[7] Ghasemi, A.; Zahediasl, S. Is nitric oxide a hormone? *Iran BioMed. J*., **2011**, *15*(3), 59-65.

[8] Gkaliagkousi, E.; Ferro, A. Nitric oxide signalling in the regulation of cardiovascular and platelet function. *Front. Biosci.,* (Landmark Ed), **2011**, *16*, 1873-1897.

[9] Lin, J.; Steenbergen, C.; Murphy, E.; Sun, J. Estrogen receptor-beta activation results in S-nitrosylation of proteins involved in cardioprotection. *Circulation*, **2009**, *120*(3), 245-254.

[10] Isgaard, J. Cardiovascular disease and risk factors: The role of growth hormone. *Horm. Res*., **2004**, *62*(Suppl 4), 31-38.

[11] Hampl, R.; Kubatova, J.; Heracek, J.; Sobotka, V.; Starka, L. Hormones and endocrine disruptors in human seminal plasma. *Endocr. Regul*., **2013**, *47*(3), 149-158.

[12] Collins, J.J. Phytotherapeutic management of endocrine dysfunctions. *Nutri. News*., **2006**.

[13] Schwartz, E. *The hormone solution: Naturally alleviate symptoms of hormone imbalance from adolescence through menopause,* 1st ed.; Grand Central Publishing: **2002**.

[14] Robert-Seilaniantz, A.; Navarro, L.; Bari, R.; Jones, J.D. Pathological hormone imbalances. *Curr. Opin. Plant Biol*., **2007**, *10*(4), 372-379.

[15] Brown, N.J. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nat. Rev. Nephrol*., **2013**, *9*(8), 459-469.

[16] Chlebowski, R.T.; Anderson, G.L. Menopausal hormone therapy and breast cancer mortality: Clinical implications. *Ther. Adv. Drug Saf*., **2015**, *6*(2), 45-56.

[17] Qian, J.; Fulton, D. Post-translational regulation of endothelial nitric oxide synthase in vascular endothelium. *Front. Physiol*., **2013**, *4*, 347.

[18] Feil, R.; Lohmann, S.M.; de Jonge, H.; Walter, U.; Hofmann, F. Cyclic GMP-dependent protein kinases and the cardiovascular system: insights from genetically modified mice. *Circ. Res*., **2003**, *93*(10), 907-916.

[19] Gonczi, M.; Papp, R.; Kovacs, M.; Seprenyi, G.; Vegh, A. Modulation of gap junctions by nitric oxide contributes to the antiarrhythmic effect of sodium nitroprusside? *Br. J. Pharmacol*., **2009**, *156*(5), 786-793.

[20] Singh, R.B.; Mengi, S.A.; Xu, Y.J.; Arneja, A.S.; Dhalla, N.S. Pathogenesis of atherosclerosis: A multifactorial process. *Exp. Clin. Cardiol*., **2002**, *7*(1), 40-53.

[21] Xu, W.; Liu, L.Z.; Loizidou, M.; Ahmed, M.; Charles, I.G. The role of nitric oxide in cancer. *Cell Res*., **2002**, *12*(5-6), 311-320.

[22] Chowdhary, S.; Ng, G.A.; Nuttall, S.L.; Coote, J.H.; Ross, H.F.; Townend, J.N. Nitric oxide and cardiac parasympathetic control in human heart failure. Clin Sci (Lond), **2002**, *102*(4), 397-402.

[23] Thai, H.M.; Do, B.Q.; Tran, T.D.; Gaballa, M.A.; Goldman, S. Aldosterone antagonism improves endothelial-dependent vasorelaxation in heart failure via upregulation of endothelial nitric oxide synthase production. *J. Card. Fail.*, **2006**, *12*(3), 240-245.

[24] von Haehling, S.; Anker, S.D.; Bassenge, E. Statins and the role of nitric oxide in chronic heart failure. *Heart Fail Rev*., **2003**, *8*(1), 99-106.

[25] Camenzind, E.; Scheerder, I.D. Local drug delivery for coronary artery disease: Established and emerging applications. 1 ed.; CRC Press: 2005.

[26] Miyao, Y.; Kugiyama, K.; Kawano, H.; Motoyama, T.; Ogawa, H.; Yoshimura, M.; Sakamoto, T.; Yasue, H. Diffuse intimal thickening of coronary arteries in patients with coronary spastic angina. *J. Am. Coll. Cardiol*., **2000**, *36*(2), 432-437.

[27] Erdmann, J.; Stark, K.; Esslinger, U.B.; Rumpf, P.M.; Koesling, D.; de Wit, C.; Kaiser, F.J.; Braunholz, D.; Medack, A.; Fischer, M.; Zimmermann, M.E.; Tennstedt, S.; Graf, E.; Eck, S.; Aherrahrou, Z.; Nahrstaedt, J.; Willenborg, C.; Bruse, P.; Braenne, I.; Nothen, M.M.; Hofmann, P.; Braund, P.S.; Mergia, E.; Reinhard, W.; Burgdorf, C.; Schreiber, S.; Balmforth, A.J.; Hall, A.S.; Bertram, L.; Steinhagen-Thiessen, E.; Li, S.C.; Marz, W.; Reilly, M.; Kathiresan, S.; McPherson, R.; Walter, U.; CardioGram; Ott, J.; Samani, N.J.; Strom, T.M.; Meitinger, T.; Hengstenberg, C.; Schunkert, H. Dysfunctional nitric oxide signalling increases risk of myocardial infarction. *Nature*, **2013**, *504*(7480), 432-436.

[28] Niu, X.; Watts, V.L.; Cingolani, O.H.; Sivakumaran, V.; Leyton-Mange, J.S.; Ellis, C.L.; Miller, K.L.; Vandegaer, K.; Bedja, D.; Gabrielson, K.L.; Paolocci, N.; Kass, D.A.; Barouch, L.A. Cardioprotective effect of beta-3 adrenergic receptor agonism: Role of neuronal nitric oxide synthase. *J. Am. Coll. Cardiol*., **2012**, *59*(22), 1979-1987.

[29] Pepke-Zaba, J.; Higenbottam, T.W.; Dinh-Xuan, A.T.; Stone, D.; Wallwork, J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet*, **1991**, *338*(8776), 1173-1174.

[30] Stokes, K.Y.; Dugas, T.R.; Tang, Y.; Garg, H.; Guidry, E.; Bryan, N.S. Dietary nitrite prevents hypercholesterolemic microvascular inflammation and reverses endothelial dysfunction. *Am. J. Physiol. Heart Circ. Physiol*., **2009**, *296*(5), H1281-1288.

[31] Peeters-Scholte, C.; Koster, J.; Veldhuis, W.; van den Tweel, E.; Zhu, C.; Kops, N.; Blomgren, K.; Bar, D.; van Buul-Offers, S.; Hagberg, H.; Nicolay, K.; van Bel, F.; Groenendaal, F. Neuroprotection by selective nitric oxide synthase inhibition at 24 hours after perinatal hypoxia-ischemia. *Stroke*, **2002**, *33*(9), 2304-2310.

[32] Tabuchi, M.; Umegaki, K.; Ito, T.; Suzuki, M.; Tomita, I.; Ikeda, M.; Tomita, T. Fluctuation of serum NO(x) concentration at stroke onset in a rat spontaneous stroke model (M-SHRSP). Peroxynitrite formation in brain lesions. *Brain Res*., **2002**, *949*(1-2), 147-156.

[33] Kolluru, G.K.; Bir, S.C.; Kevil, C.G. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing. *Int. J. Vasc. Med*., **2012**, *2012*, 918267.

[34] Tabit, C.E.; Chung, W.B.; Hamburg, N.M.; Vita, J.A. Endothelial dysfunction in diabetes mellitus: Molecular mechanisms and clinical implications. *Rev. Endocr. Metab. Disord*., **2010**, *11*(1), 61-74.

[35] Biswas, T.K. Endothelium, atherosclerosis and calcium channel blockers. *J. Indian Med. Assoc*., **2003**, *101*(7), 428-431.

[36] Wanstall, J.C.; Homer, K.L.; Doggrell, S.A. Evidence for, and importance of, cGMP-independent mechanisms with NO and NO donors on blood vessels and platelets. *Curr. Vasc. Pharmacol*., **2005**, *3*(1), 41-53.

[37] Tarin, C.; Gomez, M.; Calvo, E.; Lopez, J. A.; Zaragoza, C. Endothelial nitric oxide deficiency reduces MMP-13-mediated cleavage of ICAM-1 in vascular endothelium: A role in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol*., **2009**, *29*(1), 27-32.

[38] Rosner, D.; Stoneman, V.; Littlewood, T.; McCarthy, N.; Figg, N.; Wang, Y.; Tellides, G.; Bennett, M. Interferon-gamma induces Fas trafficking and sensitization to apoptosis in vascular smooth muscle cells via a PI3K- and Akt-dependent mechanism. *Am. J. Pathol*., **2006**, *168*(6), 2054-2063.

[39] Francois, M.; Kojda, G. Effect of hypercholesterolemia and of oxidative stress on the nitric oxide-cGMP pathway. *Neurochem. Int*., **2004**, *45*(6), 955-961.

[40] Yucel, I.; Akar, Y.; Yucel, G.; Ciftcioglu, M.A.; Keles, N.; Aslan, M. Effect of hypercholesterolemia on inducible nitric oxide synthase expression in a rat model of elevated intraocular pressure. *Vision Res*., **2005**, *45*(9), 1107-1114.

[41] Taner, C. B.; Severson, S. R.; Best, P. J.; Lerman, A.; Miller, V. M. Treatment with endothelin-receptor antagonists' increases NOS activity in hypercholesterolemia. *J. Appl. Physiol*., **2001**, *90*(3), 816-820.

[42] Genda, S.; Miura, T.; Miki, T.; Ichikawa, Y.; Shimamoto, K. K(ATP) channel opening is an endogenous mechanism of protection against the no-reflow phenomenon but its function is compromised by hypercholesterolemia. *J. Am. Coll. Cardiol*., **2002**, *40*(7), 1339-1346.

[43] Han, J.; Kim, N.; Joo, H.; Kim, E.; Earm, Y.E. ATP-sensitive K(+) channel activation by nitric oxide and protein kinase G in rabbit ventricular myocytes. *Am. J. Physiol. Heart Circ. Physiol*., **2002**, *283*(4), H1545-1554.

[44] Karamsetty, M.R.; Klinger, J.R.; Hill, N.S. Phytoestrogens restore nitric oxide-mediated relaxation in isolated pulmonary arteries from chronically hypoxic rats. *J. Pharmacol. Exp. Ther*., **2001**, *297*(3), 968-974.

[45] Taddei, S.; Virdis, A.; Ghiadoni, L.; Magagna, A.; Favilla, S.; Pompella, A.; Salvetti, A. Restoration of nitric oxide availability after calcium antagonist treatment in essential hypertension. *Hypertension*, **2001**, *37*(3), 943-948.

[46] Buzzarro, M.; Gross, I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. *Anesth. Analg*., **2006**, *102*(3), 964.

[47] Datta, B.; Tufnell-Barrett, T.; Bleasdale, R.A.; Jones, C.J.; Beeton, I.; Paul, V.; Frenneaux, M.; James, P. Red blood cell nitric oxide as an endocrine vasoregulator: A potential role in congestive heart failure. *Circulation*, **2004**, *109*(11), 1339-1342.

[48] Mungrue, I.N.; Gros, R.; You, X.; Pirani, A.; Azad, A.; Csont, T.; Schulz, R.; Butany, J.; Stewart, D.J.; Husain, M. Cardiomyocyte overexpression of iNOS in mice results in peroxynitrite generation, heart block, and sudden death. *J. Clin. Invest*., **2002**, *109*(6), 735-743.

[49] Kubo-Inoue, M.; Egashira, K.; Usui, M.; Takemoto, M.; Ohtani, K.; Katoh, M.; Shimokawa, H.; Takeshita, A. Long-term inhibition of nitric oxide synthesis increases arterial thrombogenecity in rat carotid artery. *Am. J. Physiol. Heart Circ. Physiol.*, **2002**, *282*(4), H1478-1484.

[50] Fischer, J.W.; Hawkins, S.; Clowes, A.W. Pharmacologic inhibition of nitric oxide synthases and cyclooxygenases enhances intimal hyperplasia in balloon-injured rat carotid arteries. *J. Vasc. Surg*., **2004**, *40*(1), 115-122.

[51] Stepp, D.W.; Merkus, D.; Nishikawa, Y.; Chilian, W.M. Nitric oxide limits coronary vasoconstriction by a shear stress-dependent mechanism. *Am. J. Physiol. Heart Circ. Physiol*., **2001**, *281*(2), H796-803.

[52] Cook, S. Coronary artery disease, nitric oxide and oxidative stress: the "Yin-Yang" effect-a Chinese concept for a worldwide pandemic. *Swiss Med. Wkly*., **2006**, *136*(7-8), 103-113.

[53] Saraiva, R.M.; Minhas, K.M.; Raju, S.V.; Barouch, L.A.; Pitz, E.; Schuleri, K.H.; Vandegaer, K.; Li, D.; Hare, J.M. Deficiency of neuronal nitric oxide synthase increases mortality and cardiac remodeling after myocardial infarction: Role of nitroso-redox equilibrium. *Circulation*, **2005**, *112*(22), 3415-3422.

[54] Tsutsui, M.; Nakata, S.; Shimokawa, H.; Otsuji, Y.; Yanagihara, N. Spontaneous myocardial infarction and nitric oxide synthase. *Trends Cardiovasc. Med*., **2008**, *18*(8), 275-279.

[55] Calvert, J.W.; Gundewar, S.; Jha, S.; Greer, J.J.; Bestermann, W.H.; Tian, R.; Lefer, D.J. Acute metformin therapy confers cardioprotection against myocardial infarction via AMPK-eNOS-mediated signaling. *Diabetes*, **2008**, *57*(3), 696-705.

[56] Zhang, S.Y.; Chen, G.; Wei, P.F.; Huang, X.S.; Dai, Y.; Shen, Y.J.; Chen, S.L.; Sun-Chi, C.A.; Xu, H.X. The effect of puerarin on serum nitric oxide concentration and myocardial eNOS expression in rats with myocardial infarction. *J. Asian Nat. Prod. Res*., **2008**, *10* (3-4), 373-381.

[57] Ozkul, A.; Akyol, A.; Yenisey, C.; Arpaci, E.; Kiylioglu, N.; Tataroglu, C. Oxidative stress in acute ischemic stroke. *J. Clin. Neurosci.,* **2007**, *14*(11), 1062-1066.

[58] Endres, M.; Gertz, K.; Lindauer, U.; Katchanov, J.; Schultze, J.; Schrock, H.; Nickenig, G.; Kuschinsky, W.; Dirnagl, U.; Laufs, U. Mechanisms of stroke protection by physical activity. *Ann. Neurol*., **2003**, *54*(5), 582-590.

[59] Limbourg, F.P.; Huang, Z.; Plumier, J.C.; Simoncini, T.; Fujioka, M.; Tuckermann, J.; Schutz, G.; Moskowitz, M.A.; Liao, J.K. Rapid nontranscriptional activation of endothelial nitric oxide synthase mediates increased cerebral blood flow and stroke protection by corticosteroids. *J. Clin. Invest*., **2002**, *110*(11), 1729-1738.

[60] Lock, S.; Last, J.M.; Dunea, G. *The Oxford Companion to Medicine*, 3rd ed.; Oxford University Press: **2001**; pp. 924.

[61] Le Tissier, P.R.; Hodson, D.J.; Lafont, C.; Fontanaud, P.; Schaeffer, M.; Mollard, P. Anterior pituitary cell networks. *Front. Neuroendocrinol.*, **2012**, *33*(3), 252-266.

[62] Fommei, E.; Iervasi, G. The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. *J. Clin. Endocrinol. Metab*., **2002**, *87*(5), 1996-2000.

[63] Spooner, P.H.; Thai, H.M.; Goldman, S.; Gaballa, M.A. Thyroid hormone analog, DITPA, improves endothelial nitric oxide and beta-adrenergic mediated vasorelaxation after myocardial infarction. *J. Cardiovasc. Pharmacol*., **2004**, *44*(4), 453-459.

[64] Estebanez-Perpina, E.; Arnold, L.A.; Jouravel, N.; Togashi, M.; Blethrow, J.; Mar, E.; Nguyen, P.; Phillips, K.J.; Baxter, J.D.; Webb, P.; Guy, R.K.; Fletterick, R.J. Structural insight into the mode of action of a direct inhibitor of coregulator binding to the thyroid hormone receptor. *Mol. Endocrinol*., **2007**, *21*(12), 2919-2928.

[65] Zhang, J.; Lazar, M.A. The mechanism of action of thyroid hormones. *Annu. Rev. Physiol*., **2000**, *62*, 439-466.

[66] Kuzman, J.A.; Vogelsang, K.A.; Thomas, T.A.; Gerdes, A.M. L-Thyroxine activates Akt signaling in the heart. *J. Mol. Cell Cardiol*., **2005**, *39*(2), 251-258.

[67] Carrillo-Sepulveda, M.A.; Ceravolo, G.S.; Fortes, Z.B.; Carvalho, M.H.; Tostes, R.C.; Laurindo, F.R.; Webb, R.C.; Barreto-Chaves, M.L. Thyroid hormone stimulates NO production via activation of the PI3K/Akt pathway in vascular myocytes. *Cardiovasc. Res*., **2010**, *85*(3), 560-570.

[68] Wehrens, X.H.; Lehnart, S.E.; Huang, F.; Vest, J.A.; Reiken, S.R.; Mohler, P.J.; Sun, J.; Guatimosim, S.; Song, L.S.; Rosemblit, N.; D'Armiento, J.M.; Napolitano, C.; Memmi, M.; Priori, S.G.; Lederer, W.J.; Marks, A.R. FKBP12.6 deficiency and defective calcium release channel (ryanodine receptor) function linked to exercise-induced sudden cardiac death. *Cell*, **2003**, *113*(7), 829-840.

[69] Wu, X.D.; Dai, D.Z.; Zhang, Q.P.; Gao, F. Propranolol and verapamil inhibit mRNA expression of RyR2 and SERCA in L-thyroxin-induced rat ventricular hypertrophy. *Acta Pharmacol. Sin*., **2004**, *25*(3), 347-351.

[70] Klein, I.; Ojamaa, K. Thyroid hormone and the cardiovascular system. *N. Engl. J. Med*., **2001**, *344*(7), 501-509.

[71] Dandona, P.; Aljada, A.; Mohanty, P.; Ghanim, H.; Hamouda, W.; Assian, E.; Ahmad, S. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: Evidence for an anti-inflammatory effect? *J. Clin. Endocrinol. Metab*., **2001**, *86*(7), 3257-3265.

[72] Lin, Y.; Rajala, M.W.; Berger, J.P.; Moller, D.E.; Barzilai, N.; Scherer, P.E. Hyperglycemia-induced production of acute phase reactants in adipose tissue. *J. Biol. Chem*., **2001**, *276*(45), 42077-42083.

[73] Brosnihan, K.B.; Li, P.; Figueroa, J.P.; Ganten, D.; Ferrario, C.M. Estrogen, nitric oxide, and hypertension differentially modulate agonist-induced contractile responses in female transgenic (mRen2)27 hypertensive rats. *Am. J. Physiol. Heart Circ. Physiol*., **2008**, *294*(5), H1995-2001.

[74] Han, G.; Ma, H.; Chintala, R.; Miyake, K.; Fulton, D.J.; Barman, S.A.; White, R.E. Nongenomic, endothelium-independent effects of estrogen on human coronary smooth muscle are mediated by type I (neuronal) NOS and PI3-kinase-Akt signaling. *Am. J. Physiol. Heart Circ. Physiol*., **2007**, *293*(1), H314-321.

[75] Iwakura, A.; Shastry, S.; Luedemann, C.; Hamada, H.; Kawamoto, A.; Kishore, R.; Zhu, Y.; Qin, G.; Silver, M.; Thorne, T.; Eaton, L.; Masuda, H.; Asahara, T.; Losordo, D.W. Estradiol enhances recovery after myocardial infarction by augmenting incorporation of bone marrow-derived endothelial progenitor cells into sites of ischemia-induced neovascularization via endothelial nitric oxide synthase-mediated activation of matrix metalloproteinase-9. *Circulation*, **2006**, *113*(12), 1605-1614.

[76] Kan, W.H.; Hsu, J.T.; Ba, Z.F.; Schwacha, M.G.; Chen, J.; Choudhry, M.A.; Bland, K.I.; Chaudry, I.H. p38 MAPK-dependent eNOS upregulation is critical for 17beta-estradiol-mediated cardioprotection following trauma-hemorrhage. *Am. J. Physiol. Heart Circ. Physiol*., **2008**, *294*(6), H2627-2636.

[77] Smith, A.M.; Jones, R.D.; Channer, K.S. The influence of sex hormones on pulmonary vascular reactivity: Possible vasodilator therapies for the treatment of pulmonary hypertension. *Curr. Vasc. Pharmacol*., **2006**, *4*(1), 9-15.

[78] Stirone, C.; Boroujerdi, A.; Duckles, S. P.; Krause, D. N. Estrogen receptor activation of phosphoinositide-3 kinase, AKT, and nitric oxide signaling in cerebral blood vessels: Rapid and long-term effects. *Mol. Pharmacol*., **2005**, *67*(1), 105-113.

[79] Simoncini, T.; Caruso, A.; Giretti, M. S.; Scorticati, C.; Fu, X.D.; Garibaldi, S.; Baldacci, C.; Mannella, P.; Fornari, L.; Genazzani, A. R. Effects of dydrogesterone and of its stable metabolite, 20-alpha-dihydrodydrogesterone, on nitric oxide synthesis in human endothelial cells. *Fertil. Steril*., **2006**, *86*(4 Suppl), 1235-1242.

[80] Simoncini, T.; Mannella, P.; Fornari, L.; Caruso, A.; Willis, M.Y.; Garibaldi, S.; Baldacci, C.; Genazzani, A.R. Differential signal transduction of progesterone and medroxyprogesterone acetate in human endothelial cells. *Endocrinology*, **2004**, *145*(12), 5745-5756.

[81] Simoncini, T.; Mannella, P.; Fornari, L.; Varone, G.; Caruso, A.; Genazzani, A.R. Dehydroepiandrosterone modulates endothelial nitric oxide synthesis via direct genomic and nongenomic mechanisms. *Endocrinology*, **2003**, *144*(8), 3449-3455.

[82] Molinari, C.; Battaglia, A.; Grossini, E.; Mary, D.A.; Vassanelli, C.; Vacca, G. The effect of testosterone on regional blood flow in prepubertal anaesthetized pigs. *J. Physiol.,* **2002**, *543*(Pt 1), 365-372.

[83] Fan, Y.H.; Zhao, L.Y.; Zheng, Q.S.; Dong, H.; Wang, H.C.; Yang, X.D. Arginine vasopressin increases iNOS-NO system activity in cardiac fibroblasts through NF-kappaB activation and its relation with myocardial fibrosis. *Life Sci*., **2007**, *81*(4), 327-335.

[84] Petersson, M. Cardiovascular effects of oxytocin. *Prog. Brain Res*., **2002**, *139*, 281-288.

[85] Cattaneo, M.G.; Lucci, G.; Vicentini, L.M. Oxytocin stimulates in vitro angiogenesis via a Pyk-2/Src-dependent mechanism. *Exp. Cell. Res.*, **2009**, *315*(18), 3210-3219.

[86] Jankowski, M.; Wang, D.; Hajjar, F.; Mukaddam-Daher, S.; McCann, S. M.; Gutkowska, J. Oxytocin and its receptors are synthesized in the rat vasculature. *Proc. Natl. Acad. Sci. USA*, **2000**, *97*(11), 6207-6211.

[87] Molinari, C.; Grossini, E.; Mary, D.A.; Uberti, F.; Ghigo, E.; Ribichini, F.; Surico, N.; Vacca, G. Prolactin induces regional vasoconstriction through the beta2-adrenergic and nitric oxide mechanisms. *Endocrinology*, **2007**, *148*(8), 4080-4090.

[88] Lee, S.H.; Nishino, M.; Mazumdar, T.; Garcia, G.E.; Galfione, M.; Lee, F.L.; Lee, C.L.; Liang, A.; Kim, J.; Feng, L.; Eissa, N.T.; Lin, S.H.; Yu-Lee, L.Y. 16-kDa prolactin down-regulates inducible nitric oxide synthase expression through inhibition of the signal transducer and activator of transcription 1/IFN regulatory factor-1 pathway. *Cancer Res*., **2005**, *65*(17), 7984-7992.

[89] Gonzalez, C.; Corbacho, A.M.; Eiserich, J.P.; Garcia, C.; Lopez-Barrera, F.; Morales-Tlalpan, V.; Barajas-Espinosa, A.; Diaz-Munoz, M.; Rubio, R.; Lin, S.H.; Martinez de la Escalera, G.; Clapp, C. 16K-prolactin inhibits activation of endothelial nitric oxide synthase, intracellular calcium mobilization, and endothelium-dependent vasorelaxation. *Endocrinology*, **2004**, *145*(12), 5714-5722.

[90] Odgerel, T.; Han, J.L.; Yang, C.S.; Mao, J.M. The relationship between sex hormones and extent of coronary artery disease in postmenopausal women. *Chin Med. J.,* (Engl), **2007**, *120*(1), 71-73.

[91] Takesue, K.; Hattori, M.A.; Nishida, N.; Kato, Y.; Fujihara, N. Expression of endothelial nitric oxide synthase gene in cultured porcine granulosa cells after FSH stimulation. *J. Mol. Endocrinol*., **2001**, *26*(3), 259-265.

[92] Geier, S.; Muller-Strahl, G.; Zimmer, H.G. The inotropic response of the isolated, perfused, working rat heart to norepinephrine is attenuated by inhibition of nitric oxide. *Basic Res. Cardiol*., **2002**, *97*(2), 145-152.

[93] Kelly, J.J.; Williamson, P.; Martin, A.; Whitworth, J.A. Effects of oral L-arginine on plasma nitrate and blood pressure in cortisol-treated humans. *J. Hypertens*., **2001**, *19*(2), 263-268.

[94] Kelly, J.J.; Tam, S.H.; Williamson, P.M.; Whitworth, J.A. Decreased threshold for the nitric oxide donor glyceryl trinitrate in cortisol-induced hypertension in humans. *Clin. Exp. Pharmacol. Physiol*., **2007**, *34*(12), 1317-1318.

[95] Caldarone, C.A.; McCrindle, B.W.; Van Arsdell, G.S.; Coles, J. G.; Webb, G.; Freedom, R.M.; Williams, W.G. Independent factors associated with longevity of prosthetic pulmonary valves and valved conduits. *J. Thorac. Cardiovasc. Surg*., **2000**, *120*(6), 1022-1031.

[96] Tribulova, N.; Knezl, V.; Shainberg, A.; Seki, S.; Soukup, T. Thyroid hormones and cardiac arrhythmias. *Vascul. Pharmacol*., **2010**, *52*(3-4), 102-112.

[97] Lee, S.J.; Kang, J.G.; Ryu, O.H.; Kim, C.S.; Ihm, S.H.; Choi, M.G.; Yoo, H.J.; Hong, K.S. The relationship of thyroid hormone status with myocardial function in stress cardiomyopathy. *Eur. J. Endocrinol*., **2009**, *160*(5), 799-806.

[98] Ichiki, T. Thyroid hormone and atherosclerosis. *Vascul. Pharmacol*., **2010**, *52*(3-4), 151-156.

[99] Yu, Z.; Huang, C.X.; Wang, S.Y.; Wang, T.; Xu, L. Thyroid hormone predisposes rabbits to atrial arrhythmias by shortening monophasic action period and effective refractory period: Results from an *in vivo* study. *J. Endocrinol. Invest*., **2009**, *32*(3), 253-257.

[100] Rodriguez-Gomez, I.; Sainz, J.; Wangensteen, R.; Moreno, J.M.; Duarte, J.; Osuna, A.; Vargas, F. Increased pressor sensitivity to chronic nitric oxide deficiency in hyperthyroid rats. *Hypertension*, **2003**, *42*(2), 220-225.

[101] Rodriguez-Gomez, I.; Wangensteen, R.; Moreno, J.M.; Chamorro, V.; Osuna, A.; Vargas, F. Effects of chronic inhibition of inducible nitric oxide synthase in hyperthyroid rats. *Am. J. Physiol. Endocrinol. Metab*., **2005**, *288*(6), E1252-1257.

[102] Rosmaninho-Salgado, J.; Araujo, I.M.; Alvaro, A.R.; Mendes, A.F.; Ferreira, L.; Grouzmann, E.; Mota, A.; Duarte, E.P.; Cavadas, C. Regulation of catecholamine release and tyrosine hydroxylase in human adrenal chromaffin cells by interleukin-1beta: Role of neuropeptide Y and nitric oxide. *J. Neurochem*., **2009**, *109*(3), 911-922.

[103] Young, L.H.; Ikeda, Y.; Scalia, R.; Lefer, A.M. C-peptide exerts cardioprotective effects in myocardial ischemia-reperfusion. *Am. J. Physiol. Heart Circ. Physiol*., **2000**, *279*(4), H1453-1459.

[104] Steinberg, H.O.; Paradisi, G.; Hook, G.; Crowder, K.; Cronin, J.; Baron, A.D. Free fatty acid elevation impairs insulin-mediated vasodilation and nitric oxide production. *Diabetes*, **2000**, *49*(7), 1231-1238.

[105] Ma, H.; Zhang, H.F.; Yu, L.; Zhang, Q.J.; Li, J.; Huo, J.H.; Li, X.; Guo, W.Y.; Wang, H.C.; Gao, F. Vasculoprotective effect of insulin in the ischemic/reperfused canine heart: role of Akt-stimulated NO production. *Cardiovasc. Res*., **2006**, *69*(1), 57-65.

[106] Zhao, Z.Q.; Morris, C.D.; Budde, J.M.; Wang, N.P.; Muraki, S.; Sun, H.Y.; Guyton, R.A. Inhibition of myocardial apoptosis reduces infarct size and improves regional contractile dysfunction during reperfusion. *Cardiovasc. Res*., **2003**, *59*(1), 132-142.

[107] Nathan, D. M.; Cleary, P.A.; Backlund, J.Y.; Genuth, S.M.; Lachin, J.M.; Orchard, T.J.; Raskin, P.; Zinman, B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N. Engl. J. Med*., **2005**, *353*(25), 2643-2653.

[108] Martinez, M.A.; Fernandez, N.; Climent, B.; Garcia-Villalon, A.L.; Monge, L.; Sanz, E.; Dieguez, G. Coronary effects of vasopressin during partial ischemia and reperfusion in anesthetized goats. Role of nitric oxide and prostanoids. *Eur. J. Pharmacol*., **2003**, *473*(1), 55-63.

[109] Patel, B.M.; Chittock, D.R.; Russell, J.A.; Walley, K.R. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology*, **2002**, *96*(3), 576-582.

[110] Wasson, S.; Govindarajan, G.; Reddy, H.K.; Flaker, G. The role of nitric oxide and vasopressin in refractory right heart failure. *J. Cardiovasc. Pharmacol. Ther*., **2004**, *9*(1), 9-11.

[111] Malendowicz, L.K.; Rucinski, M.; Belloni, A.S.; Ziolkowska, A.; Nussdorfer, G.G. Leptin and the regulation of the hypothalamic-pituitary-adrenal axis. *Int. Rev. Cytol*., **2007**, *263*, 63-102.

[112] White, R.E. Estrogen and vascular function. *Vascul. Pharmacol*., **2002**, *38*(2), 73-80.

[113] Howard, B.V.; Hsia, J.; Ouyang, P.; Van Voorhees, L.; Lindsay, J.; Silverman, A.; Alderman, E.L.; Tripputi, M.; Waters, D.D. Postmenopausal hormone therapy is associated with atherosclerosis progression in women with abnormal glucose tolerance. *Circulation*, **2004**, *110*(2), 201-206.

[114] Brass, L.M. Hormone replacement therapy and stroke: Clinical trials review. *Stroke*, **2004**, *35*(11 Suppl 1), 2644-2647.

[115] Wassertheil-Smoller, S.; Hendrix, S.L.; Limacher, M.; Heiss, G.; Kooperberg, C.; Baird, A.; Kotchen, T.; Curb, J.D.; Black, H.; Rossouw, J.E.; Aragaki, A.; Safford, M.; Stein, E.; Laowattana, S.; Mysiw, W.J. Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial. *JAMA*, **2003**, *289*(20), 2673-2684.

[116] Denes, P.; Larson, J.C.; Lloyd-Jones, D.M.; Prineas, R.J.; Greenland, P. Major and minor ECG abnormalities in asymptomatic women and risk of cardiovascular events and mortality. *JAMA*, **2007**, 297(9), 978-985.

[117] Falkenstein, E.; Christ, M.; Feuring, M.; Wehling, M. Specific nongenomic actions of aldosterone. *Kidney Int.,* **2000**, *57*(4), 1390-1394.

[118] Hu, C.; Rusin, C.G.; Tan, Z.; Guagliardo, N.A.; Barrett, P.Q. Zona glomerulosa cells of the mouse adrenal cortex are intrinsic electrical oscillators. *J. Clin. Invest*., **2012**, *122*(6), 2046-2053.

[119] Ohlsson, B.; Truedsson, M.; Bengtsson, M.; Torstenson, R.; Sjolund, K.; Bjornsson, E.S.; Simren, M. Effects of long-term treatment with oxytocin in chronic constipation; a double blind, placebo-controlled pilot trial. *Neurogastroenterol. Motil*., **2005**, *17*(5), 697-704.

[120] McGraw, A.P.; McCurley, A.; Preston, I.R.; Jaffe, I.Z. Mineralocorticoid receptors in vascular disease: Connecting molecular pathways to clinical implications. *Curr. Atheroscler. Rep*., **2013**, *15*(7), 340.

[121] Yagi, S.; Akaike, M.; Aihara, K.; Iwase, T.; Yoshida, S.; Sumitomo-Ueda, Y.; Ikeda, Y.; Ishikawa, K.; Matsumoto, T.; Sata, M. High plasma aldosterone concentration is a novel risk factor of cognitive impairment in patients with hypertension. *Hypertens. Res*., **2011**, *34*(1), 74-78.

[122] Jaisser, F.; Farman, N. Emerging roles of the mineralocorticoid receptor in pathology: Toward new paradigms in clinical pharmacology. *Pharmacol. Rev*., **2016**, *68*(1), 49-75.

[123] Williams, I.L.; Wheatcroft, S.B.; Shah, A.M.; Kearney, M.T. Obesity, atherosclerosis and the vascular endothelium: Mechanisms of reduced nitric oxide bioavailability in obese humans. *Int. J. Obes. Relat. Metab. Disord*., **2002**, *26*(6), 754-764.

[124] Lushchak, V.S.; H.M. *Oxidative stress - molecular mechanisms and biological effects*. InTech: 2012; pp 362.

[125] Hoffmann, A.; Gloe, T.; Pohl, U.; Zahler, S. Nitric oxide enhances de novo formation of endothelial gap junctions. *Cardiovasc. Res*., **2003**, *60*(2), 421-430.

[126] Yoo, S.Y.; Kim, J.Y. Recent insights into the mechanisms of vasospastic angina. *Korean Circ. J.*, **2009**, *39*(12), 505-511.
[127] Forstermann, U.; Sessa, W.C. Nitric oxide synthases: regulation and function. *Eur. Heart J.*, **2012**, *33*(7), 829-837, 837a-837d.
[128] Surks, H.K. cGMP-dependent protein kinase I and smooth muscle relaxation: A tale of two isoforms. *Circ. Res.*, **2007**, *101*(11), 1078-1080.
[129] Kopper, N.W.; Gudeman, J.; Thompson, D.J. Transdermal hormone therapy in postmenopausal women: A review of metabolic effects and drug delivery technologies. *Drug Des. Devel. Ther.*, **2009**, *2*, 193-202.
[130] Van Staa, T.P.; Sprafka, J.M. Study of adverse outcomes in women using testosterone therapy. *Maturitas*, **2009**, *62*(1), 76-80.
[131] Harman, S.M.; Brinton, E.A.; Cedars, M.; Lobo, R.; Manson, J.E.; Merriam, G.R.; Miller, V.M.; Naftolin, F.; Santoro, N. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric*, **2005**, *8*(1), 3-12.
[132] Madihally, S.V.; Pantelogianis, A.; Toner, M. Antiproteolytic action of orally delivered insulin using pH-responsive hydrogels in a rat burn model. *J. Surg. Res.*, **2006**, *135*(1), 187-194.
[133] Rubio, V.C.; Sanchez-Vazquez, F.J.; Madrid, J.A. Oral administration of melatonin reduces food intake and modifies macronutrient selection in European sea bass (Dicentrarchus labrax, L.). *J. Pineal Res.*, **2004**, *37*(1), 42-47.
[134] Winfield, A.K.; Graham, J.T.; Benghuzzi, H.; Tucci, M.; Cameron, J. The role of sustained delivery of corticosterone alone or in combination with antioxidants on the cardiovascular system of adult female rats. *Biomed. Sci. Instrum.*, **2003**, *39*, 353-358.
[135] Meczekalski, B.; Czyzyk, A. New forms of estrogenotherapy in postmenopausal osteoporosis. *Pol. Merkur. Lekarski*, **2009**, *27*(157), 77-80.
[136] Pugh, P.J.; Jones, R.D.; Malkin, C.J.; Hall, J.; Nettleship, J.E.; Kerry, K.E.; Jones, T.H.; Channer, K.S. Physiologic testosterone therapy has no effect on serum levels of tumour necrosis factor-alpha in men with chronic heart failure. *Endocr. Res.*, **2005**, *31*(4), 271-283.
[137] Pugh, P.J.; Jones, T.H.; Channer, K.S. Acute haemodynamic effects of testosterone in men with chronic heart failure. *Eur. Heart J.,* **2003**, *24*(10), 909-915.
[138] Pozzilli, P.; Manfrini, S.; Costanza, F.; Coppolino, G.; Cavallo, M. G.; Fioriti, E.; Modi, P. Biokinetics of buccal spray insulin in patients with type 1 diabetes. *Metabolism*, **2005**, *54*(7), 930-934.
[139] Xu, H.B.; Huang, K.X.; Zhu, Y.S.; Gao, Q.H.; Wu, Q.Z.; Tian, W.Q.; Sheng, X.Q.; Chen, Z.X.; Gao, Z.H. Hypoglycaemic effect of a novel insulin buccal formulation on rabbits. *Pharmacol. Res.*, **2002**, *46*(5), 459-467.
[140] Generex Oral-lyn. http://www.generex.com/index.php/id/270 (accessed April 23).
[141] Mueck, A.O. Hormone replacement therapy for internal risk patients. *Gynakol Geburtshilfliche Rundsch*, **2006**, *46*(4), 174-190.
[142] Rosendaal, F.R. Hormone replacement therapy and thrombotic risk: beauty is only skin deep. *Nat. Clin. Pract. Cardiovasc. Med.*, **2008**, *5*(11), 684-685.
[143] Liu, Y.; Redetzke, R.A.; Said, S.; Pottala, J.V.; de Escobar, G.M.; Gerdes, A.M. Serum thyroid hormone levels may not accurately reflect thyroid tissue levels and cardiac function in mild hypothyroidism. *Am. J. Physiol. Heart. Circ. Physiol.*, **2008**, *294*(5), H2137-2143.
[144] Breen, D.M.; Chan, K.K.; Dhaliwall, J.K.; Ward, M.R.; Al Koudsi, N.; Lam, L.; De Souza, M.; Ghanim, H.; Dandona, P.; Stewart, D.J.; Bendeck, M.P.; Giacca, A. Insulin increases reendothelialization and inhibits cell migration and neointimal growth after arterial injury. *Arterioscler. Thromb. Vasc. Biol.*, **2009**, *29*(7), 1060-1066.
[145] Chang, S.L.; Hofmann, G.A.; Zhang, L.; Deftos, L.J.; Banga, A.K. The effect of electroporation on iontophoretic transdermal delivery of calcium regulating hormones. *J. Control. Release*, **2000**, *66*(2-3), 127-133.
[146] Yoo, J.W.; Lee, C.H. Drug delivery systems for hormone therapy. *J. Control. Release*, **2006**, *112*(1), 1-14.
[147] Needle-less injections of insulin move closer to reality. http://www.prnewswire.co.uk/news-releases/needle-less-injections-of-insulin-move-closer-to-reality-154468865.html (accessed Oct 20).
[148] Weston Medical News. http://www.weston-medical.com/ (accessed Oct 20).
[149] Daddona, P.E.; Matriano, J.A.; Mandema, J.; Maa, Y.F. Parathyroid hormone (1-34)-coated microneedle patch system: Clinical pharmacokinetics and pharmacodynamics for treatment of osteoporosis. *Pharm. Res.*, **2011**, *28*(1), 159-165.
[150] Lee, J.W.; Choi, S.O.; Felner, E.I.; Prausnitz, M.R. Dissolving microneedle patch for transdermal delivery of human growth hormone. *Small*, **2011**, *7*(4), 531-539.
[151] Cormier, M.; Daddona, P.E. Macroflux technology for transdermal delivery of therapeutic proteins and vaccines. in modified-release drug delivery technology. Rathbone, M.J.; Hadgraft, J.; Roberts, M. S., Eds. Informa Healthcare: **2002**; pp 589-598.
[152] Rachon, D.; Suchecka-Rachon, K.; Hak, L.; Mysliwska, J. Effects of intranasal 17beta-estradiol administration on serum bioactive interleukin-6 and C-reactive protein levels in healthy postmenopausal women. *Menopause*, **2006**, 13(5), 840-845.
[153] Walvoord, E.C.; de la Pena, A.; Park, S.; Silverman, B.; Cuttler, L.; Rose, S.R.; Cutler, G.; Drop, S.; Chipman, J.J. Inhaled growth hormone (GH) compared with subcutaneous GH in children with GH deficiency: Pharmacokinetics, pharmacodynamics, and safety. *J. Clin. Endocrinol. Metab.*, **2009**, *94*(6), 2052-2059.
[154] Pickup, J.; Mattock, M.; Kerry, S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: Meta-analysis of randomised controlled trials. BMJ, **2002**, *324*(7339), 705.
[155] Scheuch, G.; Kohlhaeufl, M.J.; Brand, P.; Siekmeier, R. Clinical perspectives on pulmonary systemic and macromolecular delivery. *Adv. Drug Deliv. Rev.*, **2006**, *58*(9-10), 996-1008.
[156] Bosquillon, C.; Preat, V.; Vanbever, R. Pulmonary delivery of growth hormone using dry powders and visualization of its local fate in rats. *J. Control. Release*, **2004**, *96*(2), 233-244.
[157] Ramos, L.; Hicks, C.; Caminer, A.; McGregor, I.S. Inhaled vasopressin increases sociability and reduces body temperature and heart rate in rats. *Psychoneuroendocrinology*, **2014**, *46*, 46-51.
[158] Kyriakides, Z.S.; Petinakis, P.; Kaklamanis, L.; Sbarouni, E.; Karayannakos, P.; Iliopoulos, D.; Dontas, I.; Kremastinos, D.T. Intramuscular administration of estrogen may promote angiogenesis and perfusion in a rabbit model of chronic limb ischemia. *Cardiovascular Res.*, **2001**, *49*(3), 626-633.
[159] Clark, K.E.; Baker, R.S.; Lang, U. Premarin-induced increases in coronary and uterine blood flow in nonpregnant sheep. *Am. J. Obstet. Gynecol.*, **2000**, *183*(1), 12-17.
[160] Saleh, M.C.; Connell, B.J.; Saleh, T.M. Autonomic and cardiovascular reflex responses to central estrogen injection in ovariectomized female rats. *Brain Res.*, **2000**, *879*(1-2), 105-114.
[161] Gipson, D.S.; Kausz, A.T.; Striegel, J.E.; Melvin, T.R.; Astrom, L.J.; Watkins, S.L. Intraperitoneal administration of recombinant human growth hormone in children with end-stage renal disease. *Pediatr. Nephrol.*, **2001**, *16*(1), 29-34.
[162] Safer, J.D.; Crawford, T.M.; Fraser, L.M.; Hoa, M.; Ray, S.; Chen, T.C.; Persons, K.; Holick, M.F. Thyroid hormone action on skin: diverging effects of topical versus intraperitoneal administration. *Thyroid*, **2003**, *13*(2), 159-165.
[163] Dezarnaulds, G.; Fraser, I.S. Vaginal ring delivery of hormone replacement therapy-a review. *Expert Opin. Pharmacother.*, **2003**, *4*(2), 201-212.
[164] Shufelt, C.L.; Merz, C.N.; Prentice, R.L.; Pettinger, M.B.; Rossouw, J.E.; Aroda, V.R.; Kaunitz, A.M.; Lakshminarayan, K.; Martin, L.W.; Phillips, L.S.; Manson, J.E. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study. *Menopause*, **2014**, *21*(3), 260-266.
[165] Pedram, A.; Razandi, M.; Lubahn, D.; Liu, J.; Vannan, M.; Levin, E.R. Estrogen inhibits cardiac hypertrophy: role of estrogen receptor-beta to inhibit calcineurin. *Endocrinology*, **2008**, *149*(7), 3361-3369.
[166] Worda, C.; Sator, M.O.; Schneeberger, C.; Jantschev, T.; Ferlitsch, K.; Huber, J.C. Influence of the catechol-O-methyltransferase (COMT) codon 158 polymorphism on estrogen levels in women. *Hum. Reprod.*, **2003**, *18*(2), 262-266.
[167] Prentice, R.L.; Langer, R.; Stefanick, M.L.; Howard, B.V.; Pettinger, M.; Anderson, G.; Barad, D.; Curb, J.D.; Kotchen, J.; Kuller, L.; Limacher, M.; Wactawski-Wende, J. Women's Health Initiative, I. Combined postmenopausal hormone therapy and cardiovascular disease: Toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. *Am. J. Epidemiol.*, **2005**, 162(5), 404-414.

[168] Laurberg, P.; Andersen, S.; Bulow Pedersen, I.; Carle, A. Hypothyroidism in the elderly: Pathophysiology, diagnosis and treatment. *Drugs Aging*, **2005**, *22*(1), 23-38.

[169] Canonico, M.; Oger, E.; Plu-Bureau, G.; Conard, J.; Meyer, G.; Levesque, H.; Trillot, N.; Barrellier, M.T.; Wahl, D.; Emmerich, J.; Scarabin, P.Y. Estrogen; thromboembolism risk study, G. hormone therapy and venous thromboembolism among postmenopausal women: Impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation*, **2007**, *115*(7), 840-845.

[170] Stefanick, M.L. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *Am. J. Med*., **2005**, *118*(Suppl12B), 64-73.

[171] Zhang, H.; Zhang, J.; Streisand, J.B. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. *Clin. Pharmacokinet*., **2002**, *41*(9), 661-680.

[172] Lima, S.M.; Aldrighi, J.M.; Consolim-Colombo, F.M.; Mansur Ade, P.; Rubira, M.C.; Krieger, E.M.; Ramires, J.A. Acute administration of 17beta-estradiol improves endothelium-dependent vasodilation in postmenopausal women. *Maturitas*, **2005**, *50*(4), 266-274.

[173] Rosano, G.M.; Gebara, O.; Sheiban, I.; Silvestri, A.; Wajngarten, M.; Vitale, C.; Aldrighi, J.M.; Ramires, A.F.; Fini, M.; Mercuro, G. Acute administration of 17beta-estradiol reduces endothelin-1 release during pacing-induced ischemia. *Int. J. Cardiol*., **2007**, *116*(1), 34-39.

[174] Samsioe, G. Transdermal hormone therapy: Gels and patches. *Climacteric*, **2004**, 7(4), 347-356.

[175] Bhasin, S.; Parker, R.A.; Sattler, F.; Haubrich, R.; Alston, B.; Umbleja, T.; Shikuma, C.M. Effects of testosterone supplementation on whole body and regional fat mass and distribution in human immunodeficiency virus-infected men with abdominal obesity. *J. Clin. Endocrinol. Metab*., **2007**, *92*(3), 1049-1057.

[176] Margo, K.; Winn, R. Testosterone treatments: why, when, and how? *Am. Fam. Physician*, **2006**, *73*(9), 1591-1598.

[177] Perera, M.; Sattar, N.; Petrie, J.R.; Hillier, C.; Small, M.; Connell, J.M.; Lowe, G.D.; Lumsden, M.A. The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in postmenopausal women with type 2 diabetes: a randomized, placebo-controlled study. *J. Clin. Endocrinol. Metab*., **2001**, *86*(3), 1140-1143.

[178] Sherwood, A.; Bower, J.K.; McFetridge-Durdle, J.; Blumenthal, J. A.; Newby, L.K.; Hinderliter, A.L. Age moderates the short-term effects of transdermal 17beta-estradiol on endothelium-dependent vascular function in postmenopausal women. *Arterioscler. Thromb. Vasc. Biol*., **2007**, *27*(8), 1782-1787.

[179] Romano, M. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. A randomized, double-blind, placebo-controlled study. *Italian Heart J.*, **2001**, *2*(2), 203-204.

[180] Blumel, J.E.; Campodonico, I. Are transdermic estrogens cardioprotective?. *Rev. Med. Chil*., **2001**, *129*(4), 433-440.

[181] Schuchert, A.; Liebau, M.; Behrens, G.; Mueck, A.O.; Meinertz, T. Are the acute effects of transdermal estradiol in postmenopausal women with coronary disease related to changes of the autonomic tone?. *Z. Kardiol*., **2002**, *91*(2), 156-160.

[182] Shinmura, K.; Nagai, M.; Tamaki, K.; Bolli, R. Loss of ischaemic preconditioning in ovariectomized rat hearts: possible involvement of impaired protein kinase C epsilon phosphorylation. *Cardiovasc. Res*., **2008**, *79*(3), 387-394.

[183] Capan, Y.; Jiang, G.; Giovagnoli, S.; Na, K.H.; DeLuca, P.P. Preparation and characterization of poly(D,L-lactide-co-glycolide) microspheres for controlled release of human growth hormone. *AAPS PharmSciTech.*, **2003**, *4*(2), E28.

[184] Almeida, A.J.; Souto, E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. *Adv. Drug Deliv. Rev*., **2007**, *59*(6), 478-490.

[185] Transdermal drug delivery. *APBN*, **2007**, *11*(6), 336-339.

[186] Finnin, B.C.; Morgan, T.M. Transdermal penetration enhancers: applications, limitations, and potential. *J. Pharm. Sci*., **1999**, *88*(10), 955-958.

[187] Prausnitz, M.R. Microneedles for transdermal drug delivery. *Adv. Drug Deliv. Rev*., **2004**, *56*(5), 581-587.

[188] Prausnitz, M.R.; Langer, R. Transdermal drug delivery. *Nat. Biotechnol*., **2008**, *26*(11), 1261-1268.

[189] McAllister, D.V.; Wang, P.M.; Davis, S.P.; Park, J.H.; Canatella, P.J.; Allen, M.G.; Prausnitz, M.R. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies. *Proc. Natl. Acad. Sci. USA*, **2003**, *100*(24), 13755-13760.

[190] Verbaan, F.J.; Bal, S.M.; van den Berg, D.J.; Groenink, W.H.; Verpoorten, H.; Luttge, R.; Bouwstra, J.A. Assembled microneedle arrays enhance the transport of compounds varying over a large range of molecular weight across human dermatomed skin. *J. Control. Release*, **2007**, *117*(2), 238-245.

[191] Hemelaar, M.; van der Mooren, M.J.; Rad, M.; Kluft, C.; Kenemans, P. Effects of non-oral postmenopausal hormone therapy on markers of cardiovascular risk: A systematic review. *Fertil. Steril*., **2008**, *90*(3), 642-672.

[192] Bitter, C.; Suter-Zimmermann, K.; Surber, C. Nasal drug delivery in humans. *Curr. Probl. Dermatol*., **2011**, *40*, 20-35.

[193] Agu, R.U.; Ugwoke, M.I.; Armand, M.; Kinget, R.; Verbeke, N. The lung as a route for systemic delivery of therapeutic proteins and peptides. *Respir. Res*., **2001**, *2*(4), 198-209.

[194] Subramani, K. NPDDS for the treatment of diabetes. In drug delivery nanoparticles formulation and characterization, 1 ed.; Pathak, Y.; Thassu, D., Eds. CRC Press: **2009**; pp. 416.

[195] Plumley, C.J. Nanoparticle agglomeration via ionic colloidal destabilization as a novel approach to dry powder formulations for pulmonary drug delivery. Dissertations & Theses, University of Kansas, Ann Arbor, 2008.

[196] Blevins, T.; Schwartz, S.L.; Bode, B.; Aronoff, S.; Baker, C.; Kimball, K.T.; Harrist, R.B.; Donnelly, C.; Burns, L.C.; Wooldridge, A.M. A Study Assessing an Injection Port for Administration of Insulin. *Diabet. Spectrum*, **2008**, *21*(3), 197-202.

[197] Ruixing, Y.; Jiaquan, L.; Jie, C.; Dezhai, Y. Intravenous administration of vascular endothelial growth factor improves cardiac performance and inhibits cardiomyocyte apoptosis. *Growth Factors*, **2006**, *24*(3), 209-217.

[198] Kroon, L.A.; Williams, C. Diabetes Mellitus In: *Applied Therapeutics: The Clinical Use of Drugs*, 8 Eds.; Koda-Kimble, M.A.; Young, L.Y.; Kradjan, W.A.; Guglielmo, B.J.; Alldredge, B.K.; Corelli, R.L., Eds. Lippincott Williams & Wilkins: Philapedia, **2004**; pp. 3040.

[199] Caminiti, G.; Volterrani, M.; Iellamo, F.; Marazzi, G.; Massaro, R.; Miceli, M.; Mammi, C.; Piepoli, M.; Fini, M.; Rosano, G.M. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J. Am. Coll. Cardiol*., **2009**, *54*(10), 919-927.

[200] Stergiopoulos, K.; Brennan, J.J.; Mathews, R.; Setaro, J.F.; Kort, S. Anabolic steroids, acute myocardial infarction and polycythemia: A case report and review of the literature. *Vasc. Health Risk Manag*., **2008**, *4*(6), 1475-1480.

[201] Kayser, O.; Lemke, A.; Hernandez-Trejo, N. The impact of nanobiotechnology on the development of new drug delivery systems. *Curr. Pharm. Biotechnol*., **2005**, *6*(1), 3-5.

[202] Hariharan, S.; Bhardwaj, V.; Bala, I.; Sitterberg, J.; Bakowsky, U.; Ravi K.M.N. Design of estradiol loaded PLGA nanoparticulate formulations: A potential oral delivery system for hormone therapy. *Pharm. Res*., **2006**, *23*(1), 184-195.

[203] Yuan, W.; Hu, Z.; Su, J.; Wu, F.; Liu, Z.; Jin, T. Preparation and characterization of recombinant human growth hormone-$Zn^{2+}$-dextran nanoparticles using aqueous phase-aqueous phase emulsion. *Nanomedicine*, **2012**, *8*(4), 424-427.

[204] Shin, J.H.; Schoenfisch, M.H. Inorganic/organic hybrid silica nanoparticles as a nitric oxide delivery scaffold. *Chem. Mater*., **2008**, *20*(1), 239-249.

[205] Carpenter, A.W.; Schoenfisch, M.H. Nitric oxide release: part II. Therapeutic applications. *Chem. Soc. Rev*., **2012**, *41*(10), 3742-3752.

[206] Wissing, S.A.; Kayser, O.; Muller, R.H. Solid lipid nanoparticles for parenteral drug delivery. *Adv. Drug Deliv. Rev*., **2004**, *56*(9), 1257-1272.

[207] Oussoren, C.; Storm, G.; Senior, J.; Crommelin, D. Liposomes In: *Sustained-Release Injectable Products;* Senior, J.; Radomsky, M. L., Eds. Interpharm Press: Denver, **2000**; pp. 552.

[208] Davis, S.S. Coming of age of lipid-based drug delivery systems. *Adv. Drug Deliv. Rev*., **2004**, *56*(9), 1241-1242.

[209] Kisel, M.A.; Kulik, L.N.; Tsybovsky, I.S.; Vlasov, A.P.; Vorob'yov, M.S.; Kholodova, E.A.; Zabarovskaya, Z.V. Liposomes with phosphatidylethanol as a carrier for oral delivery of insulin: Studies in the rat. *Int. J. Pharm*., **2001**, *216*(1-2), 105-114.

[210] Celik, T.; Iyisoy, A.; Kursaklioglu, H.; Celik, M. The forgotten player of in-stent restenosis: Endothelial dysfunction. *Int. J. Cardiol*., **2008**, *126*(3), 443-444.

[211] Han, Y.; Liang, M.; Kang, J.; Qi, Y.; Deng, J.; Xu, K.; Yan, C. Estrogen-eluting stent implantation inhibits neointimal formation and extracellular signal-regulated kinase activation. *Catheter Cardiovasc. Interv*., **2007**, *70*(5), 647-653.

[212] Oh, B.; Lee, C.H. Advanced cardiovascular stent coated with nanofiber. *Mol. Pharm*., **2013**, *10*(12), 4432-4442.

[213] La, T.H.; Nguyen, T.T.T.; Pham, V.P.; Nguyen, T.M.H.; Le, Q.H. Using DNA nanotechnology to produce a drug delivery system. *Adv. Nat. Sci.*: *Nanosci. Nanotechnol*., **2013**, *4*(1), 015002.

[214] Ngoepe, M.; Choonara, Y.E.; Tyagi, C.; Tomar, L.K.; du Toit, L.C.; Kumar, P.; Ndesendo, V.M. K.; Pillay, V. Integration of biosensors and drug delivery technologies for early detection and chronic management of illness. *Sensors*, **2013**, *13*(6), 7680-7713.

[215] Chavakis, E.; Koyanagi, M.; Dimmeler, S. Enhancing the outcome of cell therapy for cardiac repair: progress from bench to bedside and back. *Circulation*, **2010**, *121*(2), 325-335.

[216] Perin, E.C. Stem cell therapy for cardiovascular disease. *Tex. Heart Inst. J*., **2006**, *33*(2), 204-208.

[217] Tongers, J.; Losordo, D.W.; Landmesser, U. Stem and progenitor cell-based therapy in ischaemic heart disease: Promise, uncertainties, and challenges. *Eur. Heart J*., **2011**, *32*(10), 1197-1206.

[218] Fazio, S.; Palmieri, E.A.; Lombardi, G.; Biondi, B. Effects of thyroid hormone on the cardiovascular system. *Recent Prog. Horm. Res*., **2004**, *59*, 31-50.

[219] Yang, X.P.; Reckelhoff, J.F. Estrogen, hormonal replacement therapy and cardiovascular disease. *Curr. Opin. Nephrol. Hypertens*., **2011**, *20*(2), 133-138.

[220] Ray, R.; Novotny, N.M.; Crisostomo, P.R.; Lahm, T.; Abarbanell, A.; Meldrum, D.R. Sex steroids and stem cell function. *Mol. Med*., **2008**, *14*(7-8), 493-501.

[221] Nakada, D.; Oguro, H.; Levi, B.P.; Ryan, N.; Kitano, A.; Saitoh, Y.; Takeichi, M.; Wendt, G.R.; Morrison, S.J. Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. *Nature*, **2014**, *505*(7484), 555-558.

[222] Jankowski, M.; Gonzalez-Reyes, A.; Noiseux, N.; Gutkowska, J. Oxytocin in the heart regeneration. *Recent Pat. Cardiovasc. Drug Discov*., **2012**, *7*(2), 81-87.

[223] Doust, J.; Lehman, R.; Glasziou, P. The role of BNP testing in heart failure. *Am. Fam. Physician*, **2006**, *74*(11), 1893-1898.

[224] Maisel, A. B-type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure: what's next? *Circulation*, **2002**, *105*(20), 2328-2331.

[225] Shang, C. B-type natriuretic peptide-guided therapy for perioperative medicine? *Open Heart*, **2014**, *1*(1), e000105.