Cluster of differentiation 36 (CD 36), ENac, and AQP 2 effects on heart

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Abstract. Nowadays obesity, defined as an imbalance between food intake and exercising, has become a health concern worldwide. Obesity triggers many diseases, one of them being diabetes mellitus (DM) type 2. Atherosclerosis is known to be linked with CD 36 and it can be identified as platelet integral membrane glycoprotein IV. CD 36 is known as thrombospondin-1 (TSP-1) which is found on gustatory cells, extracellular matrix (ECMs) and platelete α granules, therefore it has strong relationship with atherosclerosis. CD 36 can bind to oxLDL and induces prothrombotic state. Inspite of that, ENaC and AQP 2 also have a strong effect on heart, especially their role are often related to the heart failure (HF) because sodium and water are thought to be mediated through activation of arginine vasopression (AV), neurohormonal activity, the renal-angiotensin-aldosteron system (RAAS), and atrial natriuretic peptide that maintains cardiac output and blood pressure. This article is focused on the relationship of CD 36, ENaC, and AQP 2 effects’ on heart, including the molecular mechanism. This understanding needed to treat and to cure the heart diseases and prolong the sufferers life expectancy.

1. Introduction
There are five main taste types (salty, bitter, sour, sweet, and umami) and additional taste buds (spicy, metal, water, calcium, and fat). In this review we will discuss the relationship between salty taste receptors (ENaC), fat (CD 36), water (AQP 2), and conditions associated with metabolic syndrome (Diabetes Mellitus), heart (Heart Failure / HF) and atherosclerosis in terms of molecular, pathology, patobiophysics, and immunological responses [1].

Epidemiological studies indicate that obesity is a risk factor associated with several types of diseases, including: cardiovascular disease, kidney disease, and associated metabolic syndrome diseases which now have become epidemic problems throughout the world. Statistical data shows that around 1.1 billion people suffer from obesity. Based on these data, this article aimed to discuss significant relationships between the sensory system of taste with obesity and obesity complications associated with cardiovascular diseases such as heart failure in each receptor associated with the sensory system, such as: ENaC receptors associated with the taste of salty, CD 36 receptors associated with fat receptors, and aquaporin receptors associated with water receptors [1–3]

2. Literature Review
2.1. Concept of salty taste and its receptor (ENaC)
Desimone and Lyal, Heydarpour et al., and Ganong agreed that natrium is the main extracellular
cation found in the body fluids of all living things. In the other hand, salt is the main source of natrium
that must be available to maintain the balance of the natrium level in the human body. Salty taste is
mediated by influx of Na\textsuperscript{+} ions through natrium channels, and if the natrium channel is functioning
then the delivery of passive stimulation to pass the taste cell membrane occurs in the apical part,
therefore membrane depolarization occurs and causes the release of neurotransmitters into primary
afferent taste. The lowest threshold of salty taste that can be tasted by humans is 0.01 M. This is much
lower when compared to the lowest bitter taste threshold that can be tasted by human, 0.000008 M [4–
6].
ENaC is a specific natrium receptor found in mammals and plays a role in the process of salty taste.
There are three types of ENaC subunits in the human body, namely: ENaC sub-unit α, β, γ. ENaC is
present in sensory, non-sensory epithelial cells, and is present in the dorsal tongue. ENaC is called a
specific natrium receptor because it has epithelium that can directly transport natrium ions [1,4,7–9].

2.2. Concept of fat taste and its receptor (CD 36)
Guyton C and Hall JE stated that fat is a term used to a substance related to triglycerides and is an
essential component. Fat deficiency can cause disruption in the process of vision, growth retardation,
and cause lesions on the skin. Excess fat can also trigger some adverse effects on health and increase
the risk of death, which is caused by: obesity, diabetes, and cancer. Some chemical compounds in food
and the body that can be classified as fats (lipids) are: triglycerides, phospholipids, and cholesterol
[1,10].
One receptor that acts on fat taste discussed in this article is CD 36, which functions as a gustatory
sensor for fat, and fatty acid transporters. CD 36 is found in foliate and circumvallate papillae on the
human tongue, and CD 36 is also found in the rats tongue which can cause rats’ preference for long
chain fatty acids (LCFAs) without affecting sensitivity to bitter and sweet taste. Single nucleotide
polymorphism rs1761667 on CD 36 with A and G alleles is associated with sensitivity to detection of
fatty acids at low and high concentrations. Another CD 36 gene, namely rs15483, is also associated
with lipid perceptions in the African American population [11,12].

2.3. Concept of water taste and its receptor (AQP)
Murdiastuti, Watson et. al, and Gilberson et. al. argued that water receptors are taste receptors that can
stand alone, through a transduction mechanism in the peripheral nervous system. Water reacts to
peripheral nerve fibers gustatory area on the taste buds of the larynx which acts as extension of three
different types of cells apically in taste pore and undifferentiated basal cells. The mechanism of water
or hypoosmolaric transduction begins when water enters taste receptor cells through the aquaporin
channel. Aquaporin (AQP) is a protein of water channel in red blood cells and all tissues in human
express one or more AQP. AQP is classified into three groups; the first group (AQP 3, AQP 7, and
AQP 9), the second group (AQP 0, AQP 1, AQP 2, AQP 4, AQP 5, and AQP 6), and the third group
(AQP 8). This review will be focused in AQP 2 located in the kidney. The distribution of AQP 1 and
AQP 2 is dominantly in the basolateral membrane in taste cells. AQP 2 water channels play a role in
water movement during hyper or hypoosmotic stimulation and affect the ability of taste cells to
regulate water and respond to water to assist the tasting process and facilitate movement of water in
taste cells in order to regulate the volume of water during changes in interstitial fluid or plasma
tonicity. AQP 2 acts as a cGMPcation channel when the intracellular cGMP concentration increases,
inducing a bitter taste. It has been found that subjectively, the taste of water is influenced by the
material / substance first tasted by the tongue. If the previous substance is quinine or citric acid, the
taste of water becomes sweet, meanwhile with sodium chloride or sucrose will taste bitter. This
showed that there were significant interactions between water receptors and individual tastes [13–15].
2.4. Concept of heart disease
Heart disease is a pathophysiology condition characterized by ventricular dysfunction, associated with clinical symptoms and is the leading cause of death in the world. A decrease in systolic or diastolic pressure results in an abnormal hemodynamic circulation state, which can increase neurohormonal transition as well as water and sodium retention. The integrity of the arterial circulation is determined by two variables; cardiac output (CO) and an increase in peripheral vascular resistance. A change in one or both variables may cause a decrease of artery loading of blood, which can stimulate multiple neuro-hormonal systems to maintain adequate arterial and peripheral perfusion to vital organs. The kidneys are the main organs that regulate the decline in CO due to its essential function in maintaining body fluid volume, which is regulated by several neurohormonal systems [16,17].

3. Methods
The writing of this article as a literature review conducted by collecting data, journals related to the science of taste and heart disease, and the conclusion were drawn about the relationship between the system of taste and heart disease.

4. Discussion
4.1. Relationship between obesity and cardiovascular disease
Most common heart diseases are: atherosclerosis, hypertension and heart failure, which each disease has a relationship with the receptor taste that has been mentioned previously, namely: CD 36, ENaC, and AQP, and all three are affecting each others, even obesity is perceived as the trigger for the imbalance.

In obesity, blood glucose levels (hyperglycemia) increases and the level of fat in the blood increases (hyperlipidemia) which triggers the injury to the vascular due to the bonding between Advanced Glycation End Products (AGEs) and the AGE receptor, RAGE. AGE is a heterogeneous group of components formed by non-enzymatic glycation reactions derived from proteins, fats, and nucleic acids, which are hereinafter referred as "Millard reaction". Millard's reaction has several stages, namely: the first reaction is a reversible reaction between the carbonyl group in carbohydrate and the aminothermal group in proteins, fats, or nucleic acids which give rise to a "Schiff base" state. After that, there is a reversible rearrangement into an irreversible reaction that produces more formation of the ketoamine group which is often called "Amadori products", such as Hbs1c. Amadori products then undergo structural changes due to oxidation, dehydration and degradation which then become very stable components of AGEs. Glycation is a well-known process and occurs in post-translational modifications (PTM) with secondary products of non-enzymatic replication reactions and oxidation with AGE formation that occur in amino acids lysine, arginine, or cysteine, with the main AGE formed in vivo is AGE carboxymethyl lysine (CML). The stimulus for the formation of AGE is high blood glucose levels (glyoxal, methylglyoxal, i and 3-deoxyglucosone), the aging process that occurs in collagen and crystalline lenses. The oxidative stress process through pathological stress formation with the formation of CML-AGEs is the main key in pathological stress that occurs in the state of diabetes, aging, and chronic inflammation due to AGE, and AGE that accumulates in vivo raises and contributes to the pathology of the onset of disease [18–20].

AGE is a strong substance, but requires a receptor to carry out its functions. The receptor for AGE is RAGE which consists of several groups, namely: the AGE-R complex group (AGE-R1 (80K-H), AGE-R2 (OST-48) , and AGE-3 (galectin-3), which functions in the AGE detoxification process and contributes to the AGE inhibition process, including the glyoxalase system (GLO-1 and GLO-2) which suppresses AGE through a detoxification process at the pre-AGE stage. The second RAGE group is CD 36, as a mediator in the process of endocytosis and intracellular degradation. The last
group is RAGE, well known as the AGE receptor and the RAGE activation process starts a series of signaling cascades, which can result in cellular stress characterized by increased regulation of inflammatory mediators and failure of reparative mechanisms [19,20].

4.2. Relationship between ENaC and hypertension
On physiological and pathological conditions, the cardiovascular system can contribute to tissue repair triggered by hypertension, smoking, diabetes, and hyperlipidemia conditions, by means of vascular smooth muscle cells (VSMCs) that play a role in the process of cell migration immediately after injury to the subendothelial wall then the surface injury that will be exposed to platelets which function to growth factors and cytokines secretion. Growth factors secretion will stimulate VSMCs’s proliferation and migration from the tunica intima to the tunica media which trigger the process of neointimal tissue formation. VSMCs are an important component in blood vessels, located in the tunica media which amounts up to 40 layers in medium-sized blood vessels and 60 layers in large-sized blood vessels. The salty taste receptors (ENaC) are involved in the mechanosensory process, which mediates the vasoconstriction through VSMCs, with ENaC influenced by RAAS and insulin [21,22].

4.3. Relationship between CD 36 and atherosclerosis
The exposure of sub-endothelium to platelets in addition to induce VSMCs migration also results in the release of chemoattractant (platelet-derived growth factor/PDGF) as a trigger factor for atherosclerosis. Atherosclerosis occurs due to two factors: mechanical and biochemical damage in the sub-endothelium layer. Mechanical damage occurs due to hypertension that exceeds the ability of VSMCs to regenerate, while biochemical processes are caused by the presence of dangerous material in the blood, such as ROS formed by the results of the AGE-RAGE bond. Damaged endothelium will be thrombogenic, more permeable, and immunogenic. Immunogenic properties are the main phase of inflammation which leads to atherosclerosis, and this is related to the nature of endothelium which releases the immunoglobulin adhesion molecules and the selectin family expression: intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM -1), and endothelial-leucocyte adhesion molecule-1 (ELAM-1) [22].

Another complication that lead to atherosclerosis is an increase of cholesterol levels in the circulatory system and a number of conditions that trigger chronic vascular inflammation. At this stage, the initial and developmental stages of atherosclerosis depend on the function of the macrophages as foam cells which locally accumulate in the arterial wall and release various kinds of cytokines that induce inflammation. The formation of foam cells is primarily caused by uncontrolled uptake of low-density lipoprotein (LDL) by macrophages, which in turn triggers the accumulation of lipoprotein- excess lipid derivative in cells and induces pro-inflammatory mediators. Cellular lipid levels in foam cells are dynamically regulated by scavenger receptor (SR) cells on macrophages and cholesterol-efficient transporters, with the internalization process of oxidized LDL (oxLDL) regulated by several SR types: SR-A and CD 36 which are fat taste sensor. Several stages that can occur in atherosclerosis, in the early stage which is the earliest stage and macroscopically has not seen changes in the arterial cell wall, but microscopically in the subintima has been found a group of cells in the cytoplasm look like soap bubbles. The next stage is the stage of formation of fat lines, which at this stage occurs the foam cells build up so that it press the endothelium with a macroscopic image to see the artery wall slightly protruding into the lumen to form a spleen. The next stage is atheroma formation stage, which is characterized by the presence of foam cells and the presence of necrosis in foam cells. In the subintima, lymphocytes, smooth muscle cells, and collagen fibers are found, causing fibrous plaque. Although in a state of being pressed, the endothelial cells still look intact and a protruding abdomen is found in the lumen. The last stage in the formation of atherosclerosis is that there has been necrosis in the endothelial cells which triggers thrombus [23].
4.4. Relationship between AQP 2 between heart and kidneys disease

The state of HF will cause activation of the neurohormonal system, which consists of activation of the sympathetic nervous systems (SNS), the Renin-Angiotensin II-Aldosterone (RAAS) system, and arginine vasopressin (AVP). In the case of HF, activation of SNS is activated and there is an increase in plasma catecholamines concentrations, which play a role in maintaining blood pressure in HF conditions. SNS activation contributes to water and sodium retention in the kidneys, specifically SNS acts as a stimulant factor in renal tubules that responds to antiuretics and antinatriuretics in the absence of a glomerular filtration rate (GFR). Aquaporin water channels have decreased in the kidneys with sodium and water deficient. RAAS activation occurs in HF conditions because angiotensin II is an important mediator in water and sodium retention in patients with HF because it directly increases the water and sodium reabsorption in the renal tubules [16].

The kidneys have a series of receptors and hormones necessary for maintaining body fluid balance. Aquaporin channels contained in the kidneys are AQP 1, AQP 2, and AQP 3 with AQP 1 found in the proximal tubule and descending tubules which function in regulating urine concentration, whereas AQP 2 exclusively exists in the main cell in the collecting and connecting and AQP 3 is located in the basolateral membrane of the collecting tubules and serve as a regulation of water reabsorption which has been reabsorbed by AQP 2. Both types of AQP (AQP 1 and AQP 2) are regulated by the AVP / cyclic adenosine monophosphate (cAMP) pathway over a short-term and long-term period to increase the reabsorption of water osmosis. The state of HF causes an increase in sodium caused by increased AQP 2 work and AQP 2 RNA messenger expression. Apart from receptors, there are several transporters in the kidneys that play a critical role in sodium reabsorption, regulation of extracellular fluid volume, and increased transporter work in HF conditions. Sodium reabsorption in the renal tubule is basically associated with Na +, K + -ATPase activity which is widely present in the basolateral membrane through the nephron segment. Proximal tubules reabsorb about 2/3 of sodium, with this type also having a third type Na + / H + exchanger (NH # 3) which is responsible for sodium reabsorption in the apical part [16].

5. Conclusion

This study showed that the human taste sense are related to homeostasis disorders in the body, through the taste of saltiness (ENaC), fat (CD 36), and water (AQP 2). Homeostasis disorders that are often caused by three types of receptors are heart disease, coronary heart (atherosclerosis), hypertension, and heart failure (HF). In addition to the taste sensory receptors, several immunological products (cytokines) are known to trigger atherosclerosis (TNF-α cytokines), which affect fat deposits in the coronary arteries and body's hormonal system (RAAS), which have an influence in water reabsorption on the kidneys.

For the future research prospects, it is necessary to conduct research that can answer in a laboratory manner through experimental tests on the relationship of the three receptors with heart disease for better understanding of the molecular processes that occur between the two variables.

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