Massive amounts of regulation are constantly underway in our bodies. This regulation is brought about by using systems of communication such as the endocrine system, which uses signaling molecules called hormones as well as the receptors that bind them. It is through this kind of signaling that overall function within our bodies is achieved. One specific way that functions are regulated within our bodies is by using a vast network of receptors called peroxisome proliferator-activated receptors (PPARs), which are found in almost all tissues (1).

PPARs are nuclear receptor proteins. Nuclear receptors (NR) can be classified in many different ways, but here we will classify them as either type 1 nuclear receptors, which are located within the cytoplasm of a cell or type 2 nuclear receptors, which are located within the nucleus of a cell attached to DNA (2) (3). The nuclear receptor superfamily consists of more than 300 types of receptors, which can be further subdivided into categories based on the structure of the receptor and the ligand that binds to it (4). The main sub units of a nuclear receptor are the ligand binding domain (LBD) and the DNA binding domain (DBD) (5).

Nuclear receptors are proteins that work as transcription factors to regulate expression of genes (3) (6). When a specific ligand, which is often times a hormone, binds to the LBD of a NR a conformational change occurs. This causes the NR to change its affinity for proteins that assist in activation such as heat shock proteins as well as the NR’s ability to dimerize with other molecules needed for activation. Dimerization in addition to the conformational change causes an increased affinity for certain segments of DNA called response elements or in the case of hormone ligands,
hormone response elements (HRE). These HREs are portions of the promoter within DNA that the DBD of the NR binds to using zinc fingers and regulates gene expression (5) (3). This regulation is accomplished by recruiting other proteins that are responsible for transcribing DNA downstream from the promoter (3).

Nuclear receptors have a plethora of ligands that bind to them, and thus have a large variety of functions in gene regulation such as development, metabolism, and homeostasis (3). Some examples of nuclear receptors involved in endocrine function include steroid hormone receptors, thyroid hormone receptors, and peroxisome proliferator-activated receptors; however, PPARs play important roles in functions not limited to the endocrine system (2) (1).

PPARs can be classified into three different categories: alpha, beta/delta, and gamma, all of which are located in almost all tissues (1) (7). Like all nuclear receptors, PPARs consist of a LBD and a DBD and while their structure and function are similar, the ligands which bind to PPARs are eicosanoids and fatty acids rather than hormones (7). Even so, PPARs still function within the endocrine system by binding these ligands and affecting gene expression that involves an endocrine response (8).

There is evidence that suggests that PPARs can be located in the cytoplasm or nucleus, depending on the class of receptor and the cell it occupies, but the overall mechanism remains the same (8) (9). First, the ligand binds to the PPAR’s LBD, which induces a conformational change that causes the PPAR to shed co-repressor proteins and subsequently activate co-activator proteins. Second, the PPAR heterodimerizes with another nuclear receptor called the retinoid X receptor (RXR), which is bound to the DNA within the nucleus. In the case of PPAR, this heterodimer is bound to peroxisome proliferator hormone response elements (PPRE) of the DNA. In the presence
of ligand, the RXR sheds its co-repressor proteins as well and recruits co-activator proteins to facilitate this dimerization and subsequent attachment to the PPREs. Lastly, this complex acts as a transcription factor to regulate downstream gene expression through mechanisms such as histone modification and recruitment of RNA polymerase (1) (8) (9). By regulating gene expression, PPARs can regulate mRNA production and subsequent protein production in order to influence metabolism, inflammation, and other processes (1).

Because PPARs are nuclear receptors that bind directly to their ligand and DNA, the ligand must be hydrophobic for the ligand to be able to pass through the phospholipid bilayer of cells. This is why both of the two ligands that can activate PPARs are lipid-based. As described in the previous example, fatty acids are one of these two major endogenous ligands that can activate PPARs. We obtain fatty acids through our diets and while they are essential for cell membrane production and metabolism they also serve our bodies as these important ligands that bind to PPARs and literally control gene expression. Polyunsaturated fatty acids are the specific type of fatty acid that can be used as a PPAR ligand (7).

The other type of ligands that activate PPARs are eicosanoids. Eicosanoids are small lipids derived from arachidonic acid and can be categorized into four different groups: prostaglandins, prostacyclins, thromboxanes and leukotrienes. Arachidonic acid is derived from an essential fatty acid called linoleic acid using the delta^6^-desaturase enzyme. An enzyme called cyclooxygenase converts arachidonic acid into any of the eicosanoids. The major source of the building blocks of eicosanoids come from the phospholipid bilayer of cell membranes. The eicosanoids are synthesized and released from cells having a paracrine effect on the surrounding area. They are also locally degraded so that they have only a local effect rather than a systemic effect (10) (11).
Prostaglandins are secreted by many tissues and have a wide variety of effects ranging from smooth muscle contraction to modulation of the central nervous system. They are heavily involved in inducing inflammation and fever and inhibiting prostaglandin synthesis is a major function of NSAIDS like aspirin. Prostaglandins also stimulate the synthesis of hormones such as corticosteroids and testosterone, which implicates these eicosanoids and their PPARs as endocrine system regulators. Prostacyclins are basically another form of prostaglandins that are known as strong inhibitors of blood platelet aggregation and blood clotting (10).

Thromboxanes are eicosanoids that have a major effect on blood clotting and vascular smooth muscle regulation. Some thromboxanes are released from platelets and have an autocrine effect that then changes platelet shape and induces platelet aggregation and blood clotting. Other thromboxanes released by platelets are thought to have a paracrine effect that causes local vascular constriction, which would further enhance clotting and slow blood flow through damaged tissues (10).

Leukotrienes are synthesized by mast cells and white blood cells and are mostly released in response to injury and damaged tissue. These eicosanoids also contribute to the inflammatory response by causing vascular smooth muscle contraction and increasing vascular permeability. Leukotrienes are implicated in allergic reactions, asthma, and other disorders such as cystic fibrosis (10).

While PPARs and their ligands aren’t considered hormones or hormone receptors, it is important to reaffirm the fact that PPARs have a vital role in the endocrine system by regulating gene expression. Genes that are regulated by PPARs are either turned on or off depending on whether or not the PPAR is activated by its ligand and thus bound to the PPREs as a dimer with the
RXR. When a gene is turned on it becomes available to be transcribed into mRNA, which is then translated into a protein. These proteins can be receptors, signaling molecules or other types of proteins such as insulin receptor substrates that increase insulin sensitivity (12). This means that PPARs have a type of indirect effect on the endocrine system by either up-regulating or down-regulating the production of molecules necessary for normal endocrine function.

A prime example of PPARs’ endocrine function can be observed by studying a PPAR-gamma found in our brains. In this case, the PPARs’ ligands are fatty acids, which can be produced by a high-fat diet. With more fatty acids in the blood stream this receptor is activated and begins to regulate gene expression by up-regulating the production of certain proteins that increase hepatic insulin sensitivity and adipogenesis causing an increase in triglyceride storage and insulin sensitivity in muscle tissue (9) (13). This fat metabolism and insulin response has caused PPARs to be a major target of pharmaceuticals for controlling diseases, specifically the use of thiazolidinediones in diabetes management (1) (7).

Continued research of PPARs must be completed for us to understand more about these increasingly important nuclear receptors. Researchers are finding more and more about PPARs and their crucial part in endocrine function, inflammation, metabolism, and even cancer (9). As more research is done PPARs will be better understood, and hopefully we will be more educated as to how we can use these receptors and their variety of functions to obtain better health and more knowledge about how our body systems work together.
References: