Thesis proposal 2021: Interactions Between Omega-3, Prostaglandins and Nitric Oxide Pathways in the Management of Pulmonary Hypertension

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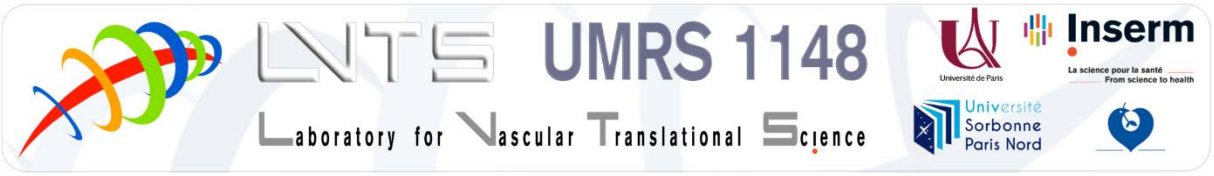

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Abstract: This thesis project concerns the field of nitric oxide, omega-3 and prostaglandins pharmacology for the benefit of elucidating the role of these chemical transmitters and respective pathways in the development of two important incapacitating diseases which are: pulmonary hypertension (PH). PH remains a major health problem despite current therapies, and in the pathophysiology, cyclooxygenase/prostaglandins and nitric oxide/cyclic guanosine monophosphate pathways play an important role in inflammation, smooth muscle relaxation and inhibition of cell proliferation. On the other hand, Omega-3 fatty acids are found mainly in fish oils and are involved in resolution of inflammation and are recently reported to be protective against cardiovascular events and bladder cancer. To our knowledge, the involvement of omega-3 fatty acids in PH and their possible interaction with the 2 deficient pathways (prostaglandins and nitric oxide) has not yet been investigated. We aim to examine whether combining modulators of these pathways (like prostacyclin mimetics and sildenafil) with omega-3 will help to optimize treatment and enhance quality of life and productivity. Using human vascular samples obtained in Bichat hospital, an array of complementary *ex-vivo/in-vitro* pharmacological studies and Western blot, Real- time PCR and/or Immunohistochemistry analyses will be applied.

Scientific objectives

Pulmonary hypertension (PH) is a disabling chronic disorder of the pulmonary vasculature, which is characterized by increased pulmonary pressure (0.3% of prevalence in the population). PH is characterized by pulmonary vascular vasoconstriction, smooth muscle cell proliferation, and thrombosis. These changes are a result of an imbalance between vasodilators (PGI2, nitric oxide (NO) Lazar et al., 2020; Ozen et al., 2020) and vasoconstrictors (thromboxane A2, endothelin, serotonin), growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic factors. Recent advances in treatment are directed at restoring the balance between these systems (Galié et al., 2016; Rabinovitch et al., 2012).

PH remains a major clinical problem despite current therapies. Among treatments, prostacyclin (PGI2, epoprostenol) and its mimetics (iloprost, treprostinil, and MRE- 269) are potent vasodilatators thought to act predominantly by activating the PGI2 receptor (IP) (Zheng et al., 2020) PGI2 is an arachidonic acid metabolite synthesized sequentially via

cyclooxygenase (COX) and prostacyclin synthase (PGIS). In general, activation of IP receptor present on smooth muscle cells by PGI2 or mimetics (also by PGE1) will increase cAMP synthesis, induce vasodilatation and inhibit cell proliferation (Norel et al. 2020; Norel, 2007).

Another treatment of PH is based on phosphodiesterase type 5 (PDE- 5) inhibitors (sildenafil, tadalafil). They have been recently introduced (Singh, 2010) and there is increasing interest in combining treatments like PGI2 mimetics with PDE- 5 inhibitors (Ventetuolo et al., 2012). Sildenafil and tadalafil act by inhibiting hydrolysis of cyclic guanosine monophosphate (cGMP which is responsible for activation of protein kinase G (PKG) and relaxations) in vasculatures which is synthesized by the action of NO on guanylate cyclase (Francis et al., 2008; 2010). Some clinical trials using a combination therapy (increasing cGMP and activating PGI2 receptor), have shown a strong beneficial effect in pulmonary hypertensive patients (Mandras et al., 2021). In contrast, the ex- vivo or in vitro studies on isolated human pulmonary vessels investigating the pharmacological mechanisms involved in such effect are rare.

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are omega-3 (n-3) polyunsaturated fatty acid found mainly in fish oils. Many studies have shown that DHA and EPA dietaries are protective against cardiovascular events like coronary artery diseases or stroke, and lowers blood pressure during hypertension (Elagizi et al., 2021; Mozaffarian and Wu, 2012). Some studies revealed that DHA metabolites (resolvins D serie, protectin and maresin) and EPA metabolites (resolvins E serie) are involved in resolution of inflammation in cardiovascular disease (Chiang and Serhan, 2020; Pirault and Back, 2018). Few in vitro studies on human vascular tone using DHA or EPA have been performed, we have recently shown in human saphenous vein that the vasoconstriction induced by noradrenaline is reduced after their pretreatment with DHA (Daci et al., 2017). In isolated human pulmonary arteries only two studies describe the effect of DHA or EPA and their metabolites on vascular tone (Jannaway et al. 2018; Morin et al., 2011). The involvement and effect of DHA or EPA in PH has not been investigated to our knowledge, as well as their possible interaction (improvement) with the 2 deficient pathways (PGI2 and NO) described above.

The cross talk between the COX and NOS pathways (enzymes responsible for the synthesis of prostanoids and nitric oxide, respectively) was initially reported in 1993 and since then, numerous studies have been undertaken to delineate the functional consequences of this interaction as well as the potential mechanism by which each pathway interacts. Although some reports show upregulation of COX activity by NO (Salvemini et al., 2013; Norel et al., 2004), others report that NO inactivates COX as demonstrated in microglial cells (Minghetti et al., 1996). On the other hand, COX activity may also be able to modulate NO synthesis since NSAIDs such as aspirin and indomethacin can significantly reduce NOS activity (Kim, 2011). It seems that the detailed mechanisms by which NO regulates prostaglandin production or vice versa is still controversial in various tissues (Kim, 2011) including pulmonary and urinary, and therefore is worth investigation; whether this modulation is cGMP &/or cAMP- dependent, or due to direct effect on NOS or COX, and which isoforms of such enzymes are involved is still not understood. The consequent implication of such interactions and how it could be optimized using DHA and EPA for better treatment of PH or OAB is to be investigated.

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