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Mitochondrial Monoamine Oxidase: Another Player in Pulmonary Hypertension?

Pulmonary hypertension (PH) is a multifactorial disease caused by pulmonary vascular remodeling, which subsequently leads to right heart hypertrophy and ultimately right heart failure. Despite major advances in therapy with specific pulmonary vasoactive substances, most forms of PH, particularly those related to precapillary vascular remodeling, remain incurable diseases. A plethora of mechanisms leading to pulmonary vascular and right heart remodeling have been described in animal models. However, the transfer of novel therapeutic concepts into the treatment of patients has so far been limited (1). Reactive oxygen species (ROS) have been suggested to play a key role in the activation of proliferative and antiapoptotic pathways underlying pulmonary vascular remodeling and also the adaptation and maladaptation of the right heart to increased afterload (2, 3). Specifically in the pulmonary endothelium, ROS may promote migration and proliferation (4). In addition, serotonin (5-hydroxytryptamine [5-HT]) has long been assigned an important role in the development of PH. This is because anorexigens, which increase the availability of 5-HT by inducing its release from platelets and inhibiting its degradation by monoamine oxidases (MAO), were noted to increase the risk of PH (5). MAOs are mitochondrial enzymes involved in production of hydrogen peroxide via the catabolism of monoamines such as catecholamines and 5-HT; thus, it is of the greatest interest to elucidate the role of MAOs for development of PH. Two isoforms of MAO exist, namely MAO-A and MAO-B, which differ in their expression among species, organs, and cell types (6). Interestingly, expression of MAO-A or MAO-B within an organ such as the heart differs with age (7), and upregulation of a specific isoform might occur under pathophysiological conditions (8).

The study in this issue of the *Journal* by Sun and colleagues (pp. 331–343) addresses this important topic and clearly demonstrates that MAO-A contributes to pulmonary vascular remodeling and intimal proliferation in the rat model of PH, induced by the VEGF-inhibitor Sugen 5416 in combination with hypoxia (SuHx) (9). The authors found a slight but significant decrease of hemodynamic parameters characterizing PH and histological features of vascular remodeling in SuHx rats treated with the selective MAO-A inhibitor clorgyline in a curative approach. Moreover, the study reveals that MAO-A does not seem to have a direct effect on right ventricular remodeling, as in the rat model of isolated right heart pressure overload induced by pulmonary artery banding, MAO-A inhibition by clorgyline did not affect right heart function or remodeling determined by hemodynamics and histology (Figure 1). Importantly, this study clarifies the role of MAO-A in the development of pulmonary vascular and right heart remodeling. In contrast to the right ventricle, the relevance of MAO-A inhibition for left ventricular pressure overload–induced heart failure and other left ventricular pathologies was previously shown in various experimental models (10). This study thus fills the gap between the right and left ventricles and provides more evidence that the right and left heart respond differently to pressure overload, as suggested by previous studies regarding the source of ROS and antioxidant defense mechanisms in right and left heart hypertrophy and failure (2, 11, 12). Moreover, this study adds another piece to the puzzle to understand the multifactorial pathogenesis of PH, and it supports previous findings that increased ROS contribute to pulmonary vascular remodeling. Over the past decade, there has been controversy in the field as to whether increased or decreased ROS promote proliferation of pulmonary vascular cells (3, 4, 13). In particular, in chronic hypoxia–induced PH, the relevance of increased ROS has recently been challenged (14). In this regard, the SuHx-PH model, in contrast to the hypoxic PH model that uses hypoxia as a single trigger, can activate other, particularly endothelium-related, mechanisms and thus may reflect human idophathic pulmonary arterial hypertension better than the hypoxia model. However, the current study is limited in this respect, as they unfortunately did not look more deeply into the mechanisms of clorgyline-dependent inhibition of pulmonary vascular remodeling. Most importantly, it did not prove the causality between MAO-A–dependent ROS release and intimal proliferation. Although clorgyline has a high specificity for MAO-A compared with MAO-B (15), other potential off-target effects of clorgyline should be addressed in further studies by use of MAO-A–deficient mice. Although the authors focused on MAO-A in the present study, which is indeed the dominant isoform under physiological conditions in the rat, a possible contribution of MAO-B, which might be upregulated under pathophysiological conditions such as hypoxia or pressure overload, was not ruled out. Thus, both the expression of MAO-B and the importance of deprenyl as a specific MAO-B inhibitor need to be assessed in future studies.

Finally, one has to ask about the relevance of the findings for human disease. Two questions are important in this regard: first, how is MAO-A regulated in human disease and what happens to MAO-B expression, and second, how robust is the therapeutic effect in the animal model? The first question needs to be answered with caution. Although the authors show increased staining of MAO-A in lung samples of PH patients by immunohistochemistry, neither in lung homogenate nor in isolated endothelial cells could upregulation of MAO-A be detected by Western blot, and MAO-B was not assessed. Using MAO-A knockout mice to test the specificity of the

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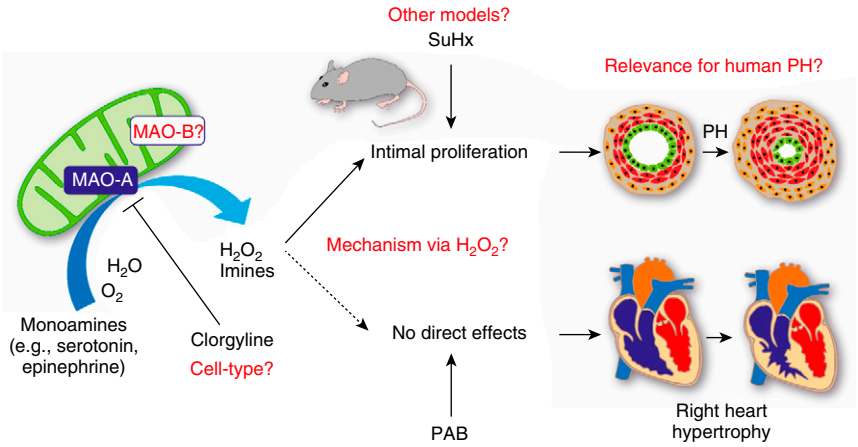

Figure 1. Monoamine oxidase A (MAO-A) is located at the outer mitochondrial membrane and catalyzes the deamination of monoamines by use of oxygen, which results in production of hydrogen peroxide. Inhibition of MAO-A by the selective, irreversible inhibitor clorgyline attenuated pulmonary hypertension (PH) in the rat model of PH, induced by the VEGF-inhibitor Sugen 5416 in combination with hypoxia (SuHx). Clorgyline did not affect right heart remodeling induced by PAB, a model that induces right heart pressure overload independent of PH. Future questions that should be addressed are related to the cell type and mechanism that underlies the protective effect of clorgyline as well as the contribution of MAO-B. Furthermore, clorgyline should be tested in other animal models of PH to test its relevance for human pulmonary arterial hypertension. PAB = pulmonary artery banding; VEGF = vascular endothelial growth factor.

antibody would also have been helpful in this regard. The second question is naturally more difficult, as animal models in general only partially reflect human disease. To address this limitation, several animal models should be used in the future to test the reproducibility of the clorgyline effect in different disease mechanisms. Moreover, the exact mechanism of clorgyline needs to be deciphered, particularly against the background that previous clinical trials inhibiting 5-HT receptors were not successful, although their study design has been questioned (1). Moreover, one has to keep in mind that clorgyline only produced a slight attenuation of PH in the current study. This finding needs to be further evaluated in other animal models that may respond more strongly to clorgyline.

Thus, the study from Sun and colleagues (9) opens a very interesting view on the role of MAO-A for development of PH and right heart remodeling, and further studies in different animal models are warranted to assess the potential of MAO-A (and/or MAO-B) inhibition for human disease. ■

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