Serotonin: a new start for an old friend?

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Understanding the mechanisms of fibrotic lung disorders, either idiopathic or associated with a specific aetiology, is the subject of a huge scientific effort in the world, sustained by both the academic pulmonary community and by pharmaceutical companies. The ultimate aim is clearly to identify one or more drugs that will have the capacity to inhibit the decline of lung function and improve survival. Such ambitious goals are unlikely to be reached from one day to another. Rather, we may expect small improvements, perhaps in subgroups of patients, which will add to improve globally the prognosis of this disease process. In the modern era of medicine, in a time in which the transmission of information is rapid and global, such a slow pace of evolution is difficult to accept and certainly contributes to the sense of nihilism sometimes affecting the respiratory community at large, including clinicians, patients and their families, who are challenging fibrotic lung disorders.

This negative feeling is also fuelled by the litany of clinical trials in patients with idiopathic pulmonary fibrosis, with negative results (trials evaluating the effect of etanercept, 1 imatinib 2 or bosentan, 3 for example), with conflicting results such as the recent CAPACITY pirfenidone trials, 4 or with minimally positive results as with sildenafil. 5 Why so many negative results? Before reaching patients, most of these molecules have been tested positive in animal models of lung fibrosis, particularly in the bleomycin-induced lung fibrosis model in rodents. This model is widely used in the scientific community to identify therapeutic targets for treating human idiopathic pulmonary fibrosis, and the question remains whether the model is the right model, or whether we should move to a better model for human disease. 6 Because of the questionable value of that model, it is absolutely necessary to confirm all results obtained in animals by data demonstrated in situ in human lung samples. This is an important point to understand the potential value of the results presented by Konigshoff and colleagues 7 in this issue of the journal. These authors should be congratulated for bringing together compelling data supporting the antifibrotic action of terugride, a 5-hydroxytryptamine 2A (5-HTR2A) and 5-hydroxytryptamine 2B (5-HTR2B) receptor antagonist. They demonstrated that these receptors are overexpressed in the fibrotic lung in humans, and that this inhibitor limits the development of fibrosis in bleomycin-induced lung fibrosis in mice and in patients. This result suggests that targeting serotonin could bring fresh air to the treatment of fibrotic lung disorders. As in other fibrotic disorders, such as liver fibrosis, 10

Altogether, these results suggest that targeting serotonin could bring fresh air to the treatment of fibrotic lung disorders. Is it time for clinical trials?

Funding

Supported by the European Commission (FP 7, European IFP Network) and by the Agence Nationale de la Recherche (ANR Physio 2006, FIBROPNEUMO).

Competing interests

None.

Provenance and peer review

Commissioned; not externally peer reviewed.


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Thorax  published online October 11, 2010

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