

COMMENTARY

Commentary on the article presented by Murdoch *et al.*

***,[1]Gilles Fillion**

[1]Neurobrologie de l'anxiéte et de la dépression, Faculty of Medicine, University of Nantes, 1 rue Gaston Veil, 44035 Nantes, France

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The experimental study reported by Murdoch *et al*. (2002) is the first demonstration that 5-HT-moduline, an endogenous tetrapeptide (Leu-Ser-Ala-Leu), can regulate the contraction of arterial smooth muscle *via* an interaction with 5-$HT_{1B/1D}$ receptors.

The specificity of the interaction between 5-HT-moduline and 5-HT_{1B} receptors was previously established in binding assays and it has been shown that 5-HT moduline acts as an allosteric modulator, having antagonistic actions at these receptors both *in vitro* and *in vivo*. Furthermore, it has been suggested that the regulatory site of action of the peptide on the 5-$HT_{1B/1D}$ receptor may be a potential target for innovative drugs.

A role for 5-HT-moduline in the regulation of cerebral activity has already been established, the release of 5-HT-moduline induced by a stimulus such as stress or physical exercise causing local desensitization of neuronal 5-$HT_{1B/1D}$ auto-receptors (Chennaoui *et al*., 2000). This pathway allows the serotonergic system to locally regulate the release of 5-HT from nerve terminals and it has been proposed that 5-HT-moduline may play a role in cerebral pathophysiology. For example, experimental results have implicated a role for the peptide in the control of anxiety (Grimaldi *et al*., 1999), a disorder known to be often related to excessive serotonergic activity of certain cerebral areas. The findings of Murdoch *et al*. (2002) form a solid experimental basis from which to explore the fascinating concept of a general regulatory role of 5-HT-moduline in the circulatory system.

As noted by the authors, 5-HT-moduline was initially isolated from brain tissues and shown to specifically interact with cerebral 5-$HT_{1B/1D}$ receptors. However, the peptide has since been shown to interact with human peripheral 5-HT_{1B} and 5-HT_{1D} receptors expressed in transfected cultured cells (Rousselle *et al*., 1998). Moreover, the presence of the peptide has been demonstrated in various peripheral tissues (heart, kidney, lung, stomach and spleen) and 5-HT-moduline has been shown to be released by the adrenal glands under various physiological conditions (Bonnin *et al*., 1999). These observations strongly suggest that the peptide has peripheral actions. However, the demonstration of a regulatory effect of 5-HT-moduline on peripheral targets was only recently reported when it was shown that the peptide affected multiplication of immunocompetent cells (Grimaldi & Fillion, 2000). Thus, the work of Murdoch *et al*. (2002) together with the previously published results, suggests that in the periphery, 5-HT-moduline may exert a similar regulatory role to that previously proposed in the brain.

An attractive hypothesis is that 5-HT-moduline may be one of the factors providing the connection between central neural activity and the periphery required to produce a global adapted response to a stimulus *in vivo*. For example, in the face of a threatening stimulus, alterations in both cerebral activity and peripheral blood flow prepare an animal to 'fight or flight'. Both central and peripheral 5-$HT_{1B/1D}$ receptors participate in these functional adaptative changes. Thus, together with previous results, the observations of Murdoch *et al*. (2002) provide a strong impetus to further explore the hypothesis that the interaction of 5-HT-moduline with 5-$HT_{1B/1D}$ receptors plays a role in the development of a co-ordinated and efficient global response of the organism to external stimuli. Moreover, they may also indicate that 5-HT-moduline could be a potential structural model for the development of innovative pharmacological tools.

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*Author for correspondence; E-mail: gilles.fillion@free.fr