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LETTER TO THE EDITOR

Clarifications on the Effects of 5-HT_{1A} Agonists and Selective 5-HT Reuptake Inhibitors on the 5-HT System

We read with great interest the article entitled: "The 5-HT1A Receptor: Signaling, Desensitization, and Gene Transcription" by P.R. Albert et al. (1996). While we agree that further studies aimed at elucidating factors controlling signaling mechanisms and genetic regulation of 5-HT_{1A} receptors may lead to a better comprehension of the effects of antidepressant/anxiolytic treatments, several clarifications/corrections have to be made so as to not lead researchers into false avenues.

First, in their introduction, the terms *down-regulation* and *desensitization* are used as synonyms. Down-regulation signifies a decrease in receptor number or density and desensitization means an attenuated function. There are numerous examples in neuropharmacology indicating that a desensitization can occur in the absence of a down-regulation and *vice versa*. The adaptability of 5-HT_{1A} receptors represents such an example. Indeed, long-term administration of 5-HT_{1A} agonists induces a desensitization of 5-HT_{1A} autoreceptors in the dorsal raphe nucleus, as assessed with electrophysiological techniques. However, such a desensitization cannot be explained solely by a down-regulation, or a "selective loss of 5-HT_{1A} autoreceptors." It has in fact been demonstrated that this attenuated function can occur in the dorsal raphe in the absence of a decrease in 5-HT_{1A} receptor density (Schechter et al. 1990). Consequently, if one investigates the factors modulating the down-regulation, he will possibly be missing the crucial factor responsible for the therapeutic effect of 5-HT_{1A} receptor agonists, that is the desensitization of 5-HT_{1A} autoreceptors.

Second, the desensitization of somatodendritic 5-HT_{1A} autoreceptors results in a *normalization* of dorsal raphe 5-HT neuronal firing activity. Indeed, no one has thus far reported that the firing activity of 5-HT neurons is increased, at least in anesthetized animals, following long-term administration of antidepressant drugs which desensitize the 5-HT_{1A} autoreceptors. Even if the acute administration of the 5-HT_{1A} antagonist spiperone can increase the firing rate of 5-HT neurons in drug-naive cats during active waking states (Jacobs and Fornal 1991), there is no evidence that the desensitization of these autoreceptors by long-term selective 5-HT reuptake inhibitors (SSRI) or 5-HT_{1A} agonists might result in such an enhancement of the firing activity of 5-HT neurons. Consequently, in the text and figure 1 of Albert et al. (1996), it should have been clear that firing activity of 5-HT neurons is probably normalized and not necessarily enhanced after a long-term treatment with SSRI or 5-HT_{1A} agonists.

Third, in figure 1 of Albert et al. (1996), the density and/or the function of the presynaptic receptor on the 5-HT terminal after a 3-week antidepressant administration is depicted as being unchanged. In the cited review (Blier et al. 1990) and in previous and subsequent publications since 1986, we have been reporting that the terminal 5-HT_{1B} autoreceptor is also desensitized by long-term administration of SSRI. This adaptative change accounts for the capacity of 5-HT neurons to release more 5-HT per action potential reaching 5-HT terminals following long-term, but not acute, administration of SSRI. These results indicate that the enhanced effectiveness of 5-HT neurotransmission following long-term SSRI treatment, rather than being directly related to reuptake blockage or directly to the desensitization of the cell body 5-HT_{1A} autoreceptor, is likely to be due to a desensitization of 5-HT autoreceptors on the terminals

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of 5-HT projections (Chaput et al. 1986). The latter desensitization has been confirmed by another group in rats (Moret and Briley 1990) and we have recently extended these observations to the guinea pig brain (Blier and Bouchard 1994), where the terminal 5-HT autoreceptor is of the 5-HT_{1D} subtype as in humans (Galzin et al. 1992).

It is also important to mention that, since the manuscript of Albert et al. (1996) was accepted for publication, we have reported that 5-HT transporters are desensitized in the raphe nuclei, the hippocampus and the cortex following long-term administration of an SSRI (Blier and Bouchard 1994; Piñeyro et al. 1994; El Mansari et al. 1995). The desensitization in the latter two brain structures appears to be due to a down-regulation of the transporters (Piñeyro et al. 1994).

These clarifications are crucial for future research endeavors in this field because, to quote Albert et al. (1996), "full understanding of the regulation of 5-HT_{1A} receptor signaling" can only be achieved if a full comprehension of the physiological changes produced by antidepressant treatments are taken as the basic premises.

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