Commentary: Chronic SSRI stimulation of astrocytic 5-HT2B receptors change multiple gene expressions/editings and metabolism of glutamate, glucose and glycogen: a potential paradigm shift

Sophie M. Banas, Silvina L. Diaz, Stéphane Doly, Arnauld Belmer, Luc Maroteaux

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Commentary: Chronic SSRI stimulation of astrocytic 5-HT$_{2B}$ receptors change multiple gene expressions/editings and metabolism of glutamate, glucose and glycogen: a potential paradigm shift

*Sophie M. Banas, Silvina L. Diaz, Stéphane Doly, Arnauld Belmer and Luc Maroteaux**

INSERM UMR S-839, Institut du Fer à Moulin, Université Pierre et Marie Curie, Paris, France

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A commentary on

Chronic SSRI stimulation of astrocytic 5-HT$_{2B}$ receptors change multiple gene expressions/editings and metabolism of glutamate, glucose and glycogen: a potential paradigm shift

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****Correspondence:***
Luc Maroteaux, luc.maroteaux@upmc.fr

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Working on the serotonin (5-hydroxytryptamine, 5-HT) 5-HT$_{2B}$ receptor since several years, we have read with high interest the review by Hertz et al. (2015). Previous studies from our group demonstrated that a direct injection in mouse raphe nucleus of the 5-HT$_{2B}$ agonist BW723C86 has the ability to increase extracellular levels of serotonin, which can be blocked by the selective 5-HT$_{2B}$ receptor antagonist RS127445 (Doly et al., 2008, 2009). We also reported that an acute injection of paroxetine 2 mg/kg in mice knocked out for the 5-HT$_{2B}$ receptor gene or in wild type mice injected with RS127445 (0.5 mg/kg) triggers a strong reduction in extracellular accumulation of 5-HT in hippocampus (Diaz et al., 2012). Following these observations, we showed that acute and chronic BW723C86 injection (3 mg/kg) can mimic the fluoxetine (3 mg/kg) and paroxetine (1 mg/kg) behavioral and biochemical antidepressant effects in mice (Diaz and Maroteaux, 2011; Diaz et al., 2012).

Hertz and coworkers used some of our published data on mice to support that fluoxetine and other SSRIs are acting as direct 5-HT$_{2B}$ receptor agonists independently of the serotonin transporter (SERT), based on their work on astrocytes. These authors forgot other important informations provided in Diaz's paper (Diaz et al., 2012), i.e., the absence of antidepressant effects of either fluoxetine or BW723C86 in mice lacking either the serotonin transporter (knockout for SERT) or differentiated serotonin neurons (knockout for Pet1). These data (i) rule out that the antidepressant effects of the 5-HT$_{2B}$ agonist BW723C86 or of fluoxetine could be independent of SERT; (ii) they indicate that serotonin neurons expressing SERT (and 5-HT$_{2B}$ receptors) are necessary for the 5-HT$_{2B}$ receptor effects independently of other cell types; (iii) they rule out the possibility that SSRIs mediate antidepressant effects only by stimulating directly putative astrocytic 5-HT$_{2B}$ receptors, which should be intact in these two mutant mice (SERT KO and Pet1 KO). A previous work (Launay et al., 2006) demonstrated a 5-HT$_{2B}$ receptor-mediated control of SERT

TABLE 1 | Affinity constants (pKi) for different binding compounds to Human 5-HT_{2C} and 5-HT_{2B} receptors.

Compounds	5-HT_{2B} Human		5-HT_{2C} Human	
	pKI	Ki (nM)	pKi	Ki (nM)
Fluoxetine[b]	<5	>10,000	6.95	112
Norfluoxetine[b]	<5	>10,000	7.04	91
Paroxetine[b]	<5	>10,000	<5	>10,000
Fluoxetine[k]	<5	>10,000	6.40 ± 0.03	400
BW723C86[k]	7.33 ± 0.03	47	7.11 ± 0.21	78

Pharmacological determinations were performed on transfected cells expressing the relevant receptor by heterologous competition. Values are from Bonhaus et al. (1997) ([b]) and Knight et al. (2004) ([k]).

activity in primary neurons from raphe nuclei, in which the BW723C86/5-HT_{2B} receptor coupling promotes phosphorylations of SERT that can easily explain our findings in mice by a direct regulation of SERT by 5-HT_{2B} receptors in a cell autonomous manner.

Furthermore, Hertz and coworkers state "The ability of all five currently used SSRIs to stimulate the 5-HT_{2B} receptor equipotentially in cultured astrocytes has been known for several years." This information originates from one of their previous observation on astrocyte cultures that "One micromolar of paroxetine, fluvoxamine or sertraline increased $cPLA_{2a}$ expression during chronic treatment; citalopram had a similar effect at 0.1–0.5 μM" (Zhang et al., 2010). Hertz and coworkers validated these data in one of their former review (Hertz et al., 2012), which reproduced their own earlier data (Kong et al., 2002), showing an half maximum effect (competition of mesulergine by fluoxetine on astrocytes) of 1 μM. However, in this review, they say that this initial calculation was "incorrect" and indicated that the Ki value of fluoxetine was in fact 70 nM on putative 5-HT_{2B} astrocytic receptors (Hertz et al., 2012). These values, which are not supported by other published experimental evidence by these authors, are divergent from all published pharmacological values obtained with identified receptors: Bonhaus et al. (1997) and Knight et al. (2004) found Ki values for cloned human 5-HT_{2B} receptors over 10 μM for fluoxetine, norfluoxetine and paroxetine (**Table 1**).

To sum up, it is clear from our experiments in mice that acute or chronic fluoxetine (and paroxetine) cannot act by a direct 5-HT_{2B} receptor stimulation independently of SERT and serotonergic neurons. Furthermore, our pharmacological determination in mice is in accordance with affinity of SSRIs for human 5-HT_{2B} receptors with Ki values over 5 μM (Diaz et al., 2012) and with no agonist activity (unpublished), while SSRI Ki values for SERT are in nanomolar range. Many SSRIs have published Ki values around 1 μM for muscarinic acetylcholine and histamine receptors or other monoamine transporters. The contribution of these other receptors/transporters in astrocytes could explain the findings of Hertz and coworkers independently of putative direct agonist effects at 5-HT_{2B} receptors. Finally, the published evidence for 5-HT_{2B} receptor expression in microglia (Krabbe et al., 2011; Kolodziejczak et al., 2015) add another level of complexity, as the concept of the tripartite synapse has recently been expanded to the monoaminergic systems to explain antidepressant drug responses (Quesseveur et al., 2013). A full set of research is still needed to understand the putative role for 5-HT in glial cells including astrocytes and/or microglia in respect to the relationship between SSRIs, serotonergic neurons and 5-HT_{2B} receptors. The needs for further research is warranted to determine how this receptor subtype contribute to SSRI antidepressant effects.

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