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1 **Commentary: Chronic SSRI stimulation of astrocytic 5-HT_{2B} receptors change multiple**
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15 **Keywords: serotonintransportergene, serotonin, neurotransmitter reuptake, depression,**
16 **mouse models, receptors, cell surface**

17
18 **A commentary on**

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20 **Chronic SSRI stimulation of astrocytic 5-HT_{2B} receptors change multiple gene**
21 **expressions/editings and metabolism of glutamate, glucose and glycogen: a potential**
22 **paradigm shift**

23 *by Hertz, L., Rothman, D. L., Li, B., and Peng, L. (2015). Front. Behav. Neurosci. 9:25. doi:*
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25
26 Working on the serotonin (5-hydroxytryptamine, 5-HT) 5-HT_{2B} receptor since several years,
27 we have read with high interest the review by Hertz et al., (Hertz et al., 2015). Previous
28 studies from our group demonstrated that a direct injection in mouse raphe nucleus of the 5-
29 HT_{2B} agonist BW723C86 has the ability to increase extracellular levels of serotonin, which
30 can be blocked by the selective 5-HT_{2B} receptor antagonist RS127445 (Doly et al., 2008;Doly
31 et al., 2009). We also reported that an acute injection of paroxetine 2 mg/kg in mice knocked
32 out for the 5-HT_{2B} receptor gene or in wild type mice injected with RS127445 (0.5 mg/kg)
33 triggers a strong reduction in extracellular accumulation of 5-HT in hippocampus (Diaz et al.,
34 2012). Following these observations, we showed that acute and chronic BW723C86 injection
35 (3 mg/kg) can mimic the fluoxetine (3 mg/kg) and paroxetine (1 mg/kg) behavioral and
36 biochemical antidepressant effects in mice (Diaz and Maroteaux, 2011;Diaz et al., 2012).

37 Hertz and coworkers used some of our published data on mice to support that
38 fluoxetine and other SSRIs are acting as direct 5-HT_{2B} receptor agonists independently of the
39 serotonin transporter (SERT), based on their work on astrocytes. These authors forgot other
40 important informations provided in Diaz's paper (Diaz et al., 2012), ie the absence of
41 antidepressant effects of either fluoxetine or BW723C86 in mice lacking either the serotonin
42 transporter (knockout for SERT) or differentiated serotonin neurons (knockout for Pet1).
43 These data (i) rule out that the antidepressant effects of the 5-HT_{2B} agonist BW723C86 or of
44 fluoxetine could be independent of SERT; (ii) they indicate that serotonin neurons expressing
45 SERT (and 5-HT_{2B} receptors) are necessary for the 5-HT_{2B} receptor effects independently of
46 other cell types; (iii) they rule out the possibility that SSRIs mediate antidepressant effects
47 only by stimulating directly putative astrocytic 5-HT_{2B} receptors, which should be intact in
48 these two mutant mice (SERT KO and Pet1 KO). A previous work (Launay et al., 2006)
49 demonstrated a 5-HT_{2B} receptor-mediated control of SERT activity in primary neurons from
50 raphe nuclei, in which the BW723C86/5-HT_{2B} receptor coupling promotes phosphorylations

51 of SERT that can easily explain our findings in mice by a direct regulation of SERT by 5-
52 HT_{2B} receptors in a cell autonomous manner.

53 Furthermore, Hertz and coworkers state "The ability of all five currently used SSRIs to
54 stimulate the 5-HT_{2B} receptor equipotentially in cultured astrocytes has been known for
55 several years". This information originates from one of their previous observation on
56 astrocyte cultures that "One micromolar of paroxetine, fluvoxamine or sertraline increased
57 cPLA_{2a} expression during chronic treatment; citalopram had a similar effect at 0.1–0.5 μM"
58 (Zhang et al., 2010). Hertz and coworkers validated these data in one of their former review
59 (Hertz et al., 2012), which reproduced their own earlier data (Kong et al., 2002), showing an
60 half maximum effect (competition of mesulergine by fluoxetine on astrocytes) of 1 μM.
61 However, in this review, they say that this initial calculation was "incorrect" and indicated
62 that the Ki value of fluoxetine was in fact 70 nM on putative 5-HT_{2B} astrocytic receptors
63 (Hertz et al., 2012). These values, which are not supported by other published experimental
64 evidence by these authors, are divergent from all published pharmacological values obtained
65 with identified receptors: Bonhaus et al., (Bonhaus et al., 1997) and Knight, (Knight et al.,
66 2004) found Ki values for cloned human 5-HT_{2B} receptors over 10 μM for fluoxetine,
67 norfluoxetine and paroxetine (**Table**).

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70 To sum up, it is clear from our experiments in mice that acute or chronic fluoxetine
71 (and paroxetine) cannot act by a direct 5-HT_{2B} receptor stimulation independently of SERT
72 and serotonergic neurons. Furthermore, our pharmacological determination in mice is in
73 accordance with affinity of SSRIs for human 5-HT_{2B} receptors with Ki values over 5 μM
74 (Diaz et al., 2012) and with no agonist activity (unpublished), while SSRI Ki values for SERT
75 are in nanomolar range. Many SSRIs have published Ki values around 1 μM for muscarinic
76 acetylcholine and histamine receptors or other monoamine transporters. The contribution of
77 these other receptors/transporters in astrocytes could explain the findings of Hertz and
78 coworkers independently of putative direct agonist effects at 5-HT_{2B} receptors. Finally, the
79 published evidence for 5-HT_{2B} receptor expression in microglia (Krabbe et al.,
80 2011; Kolodziejczak et al., 2015) add another level of complexity, as the concept of the
81 tripartite synapse has recently been expanded to the monoaminergic systems to explain
82 antidepressant drug responses (Quesseveur et al., 2013). A full set of research is still needed
83 to understand the putative role for 5-HT in glial cells including astrocytes and/or microglia in
84 respect to the relationship between SSRIs, serotonergic neurons and 5-HT_{2B} receptors. The
85 needs for further research is warranted to determine how this receptor subtype contribute to
86 SSRI antidepressant effects.

87

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96

97 **Disclosures**

98 None.

99

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Table-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., (Bonhaus et al., 1997) (^b) and Knight, (Knight et al., 2004) (^k).

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