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LETTER TO THE EDITOR

CINP

# An enhancement of the firing activity of dopamine neurons as a common denominator of antidepressant treatments?

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We read with great interest the article by West & Weiss (2011), reporting that long-term administration of antidepressant medications and repeated electroconvulsive shocks increase the firing rate of dopamine (DA) neurons in the ventral tegmental area (VTA), and to a lesser extent the percentage of spikes occurring in bursts. At first glance, these findings appear remarkably striking and seem to provide a unifying link for the antidepressant response. A closer examination of the methodology reveals, however, significant factors that may have prematurely led to such a conclusion.

A first look at the data reveals that the mean firing rate of the VTA DA neurons in their two control groups are approximately half of those reported over the past decades (2.0–2.5 Hz *vs.* 3.5–5 Hz) by our group (Chenu *et al.* 2009; Chernoloz *et al.* 2009; Dremencov *et al.* 2009; El Mansari *et al.* 2008; Ghanbari *et al.* 2009; Guiard *et al.* 2011; Katz *et al.* 2010) and by several other groups (Floresco *et al.* 2001; Franberg *et al.* 2009; Gill *et al.* 2011; Lodge & Grace, 2011; Melis *et al.* 2009; Moore *et al.* 2001; Tan *et al.* 2009; Valenti & Grace, 2010). In fact, we did not find any peer-reviewed article reporting such a low mean firing rate of VTA DA neurons in control rats. Since most researchers have used rats in the 250–350 g range, *vs.* 550–700 g in the work by West & Weiss (2011), it is thus possible that the age of the rats may have been a contributory factor to this difference. These investigators observed an apparent increase in the firing rate of DA neurons following a 14-d regimen of bupropion at 10 mg/kg.d, whereas El Mansari *et al.* (2008) reported an unaltered mean firing rate with a similar regimen, but at a dose of 30 mg/kg.d. Consequently, the dose of bupropion may have been a contributory factor, as argued by West & Weiss (2011).

Prompted by such differences between these reports, an experimental series was undertaken to explore these discrepancies. Rats weighing 500–700 g were administered bupropion at a regimen of 10 mg/kg.d for 14 d using osmotic minipumps. Recordings were carried out under chloral hydrate anaesthesia as described previously (Chenu *et al.* 2009).

The mean firing rates of DA neurons were not statistically different in controls *vs.* bupropion-treated rats using a two-tailed Student's $t$ test ($p = 0.35$). The percentages of spikes occurring in bursts were identical in the controls and the treated group (see Fig. 1).

The results of these repeat experiments first eliminate the age of the rats as a contributory factor between the differential firing rates of DA neurons in the study by West & Weiss (2011) and the results of numerous other groups in control rats. Second, the different dose regimens of bupropion also appear not to contribute to the lack of effect of this antidepressant on DA neurons in the VTA (El Mansari *et al.* 2008). Therefore, other factors must have been at play in the dataset reported by West & Weiss (2011).

The first likely possibility is the fact that West & Weiss (2011) extended the customary range neuronal firing used to identify DA neurons in the VTA to include neurons firing as low as 0.1 Hz. Indeed, Grace and co-workers over the last three decades have used a lower range of 0.5–1 Hz. Indeed they have shown that of 597 cells only three had a firing rate lower than 1 Hz (Grace & Bunney, 1984). Furthermore, in an attempt to differentiate DA from non-DA neurons in the VTA, Ungless *et al.* (2004), using tyrosine hydroxylase labelling, reported that the DA neurons had a mean firing rate of $4.6 \pm 0.2$ Hz (range 1.6–5.9 Hz) *vs.* that of non-DA neurons firing on average $2.6 \pm 1.1$ Hz (range 0.3–7.7 Hz), the latter being similar to that of the neurons reported in the control groups of West & Weiss (2011). A second possibility is that few treatment-naive rats were studied in the control groups *vs.* the numerous experimental groups (16 treatment-exposed groups). One can question when the control rats were studied with respect to the experimental animals.

In their discussion, West & Weiss (2011) misinterpreted the results of a prior study carried out with prolonged antidepressant drugs. They stated that the

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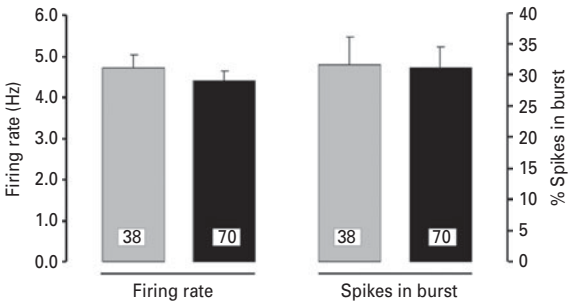


**Fig. 1.** Effect of bupropion treatment (14 d) on the firing activity of ventral tegmental area DA neurons. Data are expressed as means ± S.E.M. of the firing rate and of the percentage of spikes occurring in bursts. The number of neurons recorded in each group is provided within the histograms. Data were analysed by a *t* test. No significant effect of bupropion (■) compared to control group (□) was observed.

non-selective monoamine oxidase inhibitor (MAOI) phenelzine, used exactly as in their protocol, did not increase the firing rate of DA neurons in the article by Chenu *et al.* (2009). Actually, this prior paper described a significant decrease in firing rate with phenelzine, as well as with clorgyline, a selective type A MAOI with antidepressant properties.

Finally, no potential mechanisms were proposed for the apparent enhancement of firing of DA neurons with all the treatments used by West & Weiss (2011). In contrast, it was reported that the serotonin reuptake inhibitor escitalopram and the MAOI clorgyline inhibit the firing rate of DA neurons by the activation of 5-$HT_{2C}$ and 5-$HT_3$ receptors, respectively, because the attenuation was reversed by selective antagonists for these receptors (Chenu *et al.* 2009; Dremencov *et al.* 2009). It is noteworthy that the dose of escitalopram used in the latter experiments produces plasma levels in rats that are similar to those obtained in humans with this drug, as reported by West *et al.* (2009). Consequently, their explanation for our group failing to see an increase in the number of spontaneously active cells per track with escitalopram and citalopram because the dose was 10–20 times higher than that used by Sekine *et al.* (2007) is clinically irrelevant.

On the basis of the above-mentioned observations and the current literature, it thus appears that antidepressant treatments may not affect the function of DA neurons in a consistent manner.

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None.

## Statement of Interest

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