Effects of chronic antidepressant drug administration and electroconvulsive shock on activity of dopaminergic neurons in the ventral tegmentum: a reply to Chenu et al. (2011)

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We have read the letter commenting on our article entitled ‘Effects of chronic antidepressant drug administration and electroconvulsive shock on activity of dopaminergic neurons in the ventral tegmentum’. We offer the following response.

The authors of the letter direct attention to our mean spontaneous firing rate for dopaminergic neurons in the ventral tegmental area (VTA-DA neurons) being lower than typically found and particularly note that we included neurons with firing rates as low as 1.0 Hz. Our mean rates of firing are indeed somewhat lower than often reported by other investigators. We were clearly aware of this, specifically describing in our Methods section that we included slow-firing neurons. Our criteria for DA neurons in the VTA depended upon (a) stereotaxic location and then (b) the specific wave form of the unit as stated in the Procedure section, which is widely acknowledged for these neurons. Because we were recording multiple neurons in each animal, there was no way to mark individual neurons and identify their locations and/or characteristics histologically; consequently, we included neurons based on waveform. Given these criteria, we saw no basis for discarding neurons because their firing rate was slow and, consequently, such neurons were included.

The writers of the letter call attention to an article by Ungless et al. (2004), who described differences between DA and non-DA neurons in the VTA. The writers noted that our mean spontaneous firing rate was closer to that of non-dopaminergic cells than dopaminergic cells. However, the main point of the article by Ungless et al. was that VTA-DA neurons were inhibited by aversive or stressful stimuli whereas non-DA neurons were excited by such stimuli; they reported 10 of 12 DA neurons were inhibited by 10-s foot pinch whereas four of six non-DA neurons were excited by this stimulus. We have examined the effects of foot pinch on VTA-DA cell activity, using our standard paw compression (PC) of 1.0 s duration that elicits sensory-evoked burst firing of locus coeruleus (LC) neurons. In a study of normal rats and one of our selectively bred rat lines, we recorded from a total of 170 VTA-DA units; for each unit, response to PC was determined. Of the 170 units, spontaneous firing of 103 units was clearly inhibited by PC, while four units showed excitation. (Incidentally, this study was carried out and completely scored prior to our seeing the findings of Ungless et al., so these results could not have been biased by their findings.) Thus, the ‘inhibition versus excitation criteria’ of Ungless et al. indicates that we record overwhelmingly from DA neurons in the VTA. Finally, on some occasions (although not often), we have injected apomorphine at the conclusion of an experiment and observed that this shut down the activity of putative VTA-DA neurons, as would be expected from dopaminergic units. We continue to believe that, regardless of our mean rate of firing having been somewhat lower than that reported by others, we still have no basis for excluding neurons that meet appropriate criteria.

In regard to rate of firing, we have observed that neurons in different regions of the VTA have different firing rates. In particular, a horizontal band of VTA-DA neurons near the ventral limit of the VTA characteristically fires at a high rate (4–5 Hz or higher) and a high percentage of spikes in bursts. If one were to focus on this subpopulation, the average firing rate indeed would be higher than the values we reported. Without a detailed histological analysis, it is impossible to know the extent to which this scenario might explain apparent discrepancies.

Other possibilities that might explain differences in firing rate relate to the particular animals we use. Our
animals are bred and raised in our vivarium, having been maintained for many generations in this location. Originally derived from Charles River (USA) outbred Sprague-Dawley rats, with new animals from Charles River periodically introduced into this breeding stock, nevertheless we cannot rule out that our animals differ somewhat from those available through commercial suppliers. Also, our animals, being in residence here, have not been exposed to the stressor of being shipped from a supplier before study. Stressors can have effects long after the stressful event has occurred (e.g. Blugeot et al. 2011). Typically, investigators allow some time – i.e. days or up to weeks – after shipping before conducting experiments, but this does not insure that this stressor has not affected the animals. Finally, because we maintain our own animals here, we are readily able to use fully mature male rats aged 5–7 months, weighing 550–750 g, which have been characterized by a knowledgeable authority as being ‘young … of full adulthood’ (Nadon, 2006). For economic reasons that are perfectly understandable and with which we sympathize, almost all other investigators work with animals that are quite young, often ranging in age from 60 to 90 d. The investigators who contributed the letter assessed firing of VTA-DA neurons in animals of similar age to the ones we use and report firing rates considerably higher than our mean firing rates and consistent with what they have otherwise found in younger animals. While we do not dispute this, their sample of such animals is obviously small and it should not be ruled out that across a large population of older, fully mature rats the firing rate might be lower than in young rats typically used in other experiments.

In their letter, the investigators who commented on our article focused attention on a difference with regard to effects of a single drug, bupropion, which they have also reported effects of. The study they describe in their letter tested the same dose that we used in rats of similar age and they did not find the same effect that we reported; thus, the findings do indeed differ with regard to this drug. We do note, however, that our article reports effects of eight antidepressant drugs and ECS produce (for review, see West et al. 2009), indeed will give rise to increased VTA-DA activity, in accord with this hypothesis. Recently, we have found additional evidence supporting the influence of LC on VTA-DA activity, observing in one of our selectively bred rat lines that readily consume alcohol that alcohol markedly inhibited burst firing of their LC neurons and observed this to be accompanied by a large increase in spontaneous firing rate and burst firing of their VTA-DA neurons. To state that the paper under consideration here offered no suggestion of a mechanism for changes
in VTA-DA activity is simply erroneous and does not take into consideration what is stated in the paper.

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Statement of Interest

None.

References


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