Sir, The comprehensive analysis of striatal cannabinoid receptors in Huntington’s disease by Blázquez et al., 2011 raises some important issues of methodology. One major part of the study is the effect of CB1 receptor activation by Δ9-tetrahydrocannabinol (THC) on Huntington’s disease neuropathy. To do this, the authors compare tissue derived from R6/2 mice treated either with THC or vehicle only. For each marker investigated in Fig. 4 (GAD67, synaptophysin and PSD95), THC treatment is shown to reverse loss of immunoreactivity for marker compared to the vehicle control. However, the loss of the marker reported for PSD95 in the vehicle group does not match immunoreactivity for a similar control group, namely CB1 +/+ R6/2 mice, shown in Fig. 2, where no loss of PSD95 is reported.

This raises the possibility that the vehicle exacerbates the Huntington’s disease neuropathy. It is not clear why this should be the case when (i) no loss of PSD95 is reported for vehicle treated wild-type mice; and (ii) vehicle treatment does not change the levels of the other neuronal markers. Therefore, this result implies a highly specific effect; induced loss of a postsynaptic marker by an otherwise benign vehicle seen only in R6/2 mice. Alternatively, the explanation may lie in the methods used to analyse expression of PSD95 in this experiment, since there appears to be a qualitative difference in immunofluorescence for PSD95 between Figs 2 and 4. In Fig. 2, PSD95 immunofluorescence is intense and occurs in discrete, large fibres and cell-like structures; whereas in Fig. 4, immunofluorescence is diffuse and granulated. This qualitative difference in immunofluorescence for the same marker is again seen for GAD67. However, the qualitative difference in the pattern of immunoreactivity for GAD67 is not reflected by any quantitative difference in marker expression.

Further to this, messenger RNA for both GAD67 and PSD95 are not significantly altered in R6/2 mice compared to the wild-type. Although the finding that messenger RNA for these markers is greatly reduced in CB1-/-R6/2 mice is highly significant, this result raises further questions about the reliability of the comparisons that use immunolabelling, upon which conclusions for a beneficial effect on Huntington’s disease neuropathy by THC treatment are based. Given these points, the amelioration of behavioural symptoms of Huntington’s disease in R6/2 mice from THC treatment reported in Fig. 3 may need further consideration. These points are important if cannabinoids are to be considered as a clinical treatment for Huntington’s disease, and require further discussion.

Reference