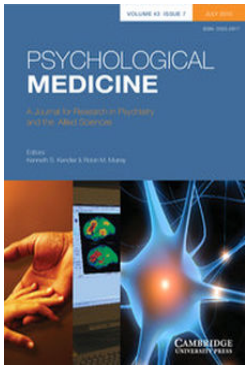

Letter to the Editor: Haloperidol but not dopamine rapidly induces neuronal death: comments on 'A systematic review of the effects of antipsychotic drugs on brain volume'

PHILLIP GRANT

Psychological Medicine / Volume 43 / Issue 07 / July 2013, pp 1568 - 1568
DOI: 10.1017/S0033291713001001, Published online: 07 May 2013

Psychological Medicine (2013), **43**, 1568.

Correspondence

Psychological Medicine, **43** (2013).
doi:10.1017/S0033291713001001
First published online 7 May 2013

Letter to the Editor

Haloperidol but not dopamine rapidly induces neuronal death: comments on 'A systematic review of the effects of antipsychotic drugs on brain volume'

In a systematic review published in *Psychological Medicine*, Moncrieff & Leo (2010) come to the conclusion that antipsychotics may be partly responsible for reductions in brain volume. Similar conclusions are reached by other reviewers, such as Navari & Dazzan (2009) and Zipursky *et al.* (2012), whereby they additionally propose that first-generation antipsychotics (FGAs) make an impact on brain volume more strongly than second-generation antipsychotics (SGAs).

All three papers, however, call for more research into the mechanisms that actually convey these effects. Although Moncrieff & Leo (2010) and Navari & Dazzan (2009) both suggest a potential neurotoxic effect of FGAs, they cite little research that may support the supposition of FGA neurotoxicity on the neuronal (i.e. the effects on the neuron) rather than solely the neural (i.e. the effects on the brain) or phenotypical level.

Noh *et al.* (2000) reported the dose-dependent induction of apoptosis through haloperidol in primary (not cell lines) mixed (neurons and glia) cortical cell cultures. These findings prove the neurotoxicity of haloperidol, but do not eliminate similar effects of increased dopamine levels (comparing healthy *versus* sick brains). Taking this into account, we replicated these results (Grant, 2011), but additionally compared effects of dopamine incubation. We found a drastic dose-dependent induction of neuronal death (90% at highest concentrations) after 24 h in haloperidol-treated but not in dopamine-treated primary mixed cortical cultures. Additionally, we examined possible mediators of haloperidol neurotoxicity, finding substantial increases in indicators of oxidative stress. These findings mirror significant increases in oxidative damage markers found in animals induced by haloperidol but not by SGAs (e.g. Parikh *et al.* 2003) as well as in schizophrenic patients (e.g. Zhang *et al.* 2006).

I would, therefore, draw two conclusions. First, haloperidol is indeed toxic at the neuronal level. Second, I believe that findings on the cell biology of schizophrenia and related factors may be of great importance and should therefore be incorporated into the field of schizophrenia research more than they currently are.

Declaration of Interest

None.

References

Grant P (2011). Dopamine neurotoxicity, oxidative stress and schizophrenia: *in vitro* and *in vivo* studies of peroxisomal reactions to increased dopamine. Doctoral thesis, Justus-Liebig-Universität Giessen (geb.uni-giessen.de/geb/volltexte/2011/8495/index.html). Accessed April 2013.

Moncrieff J, Leo J (2010). A systematic review of the effects of antipsychotic drugs on brain volume. *Psychological Medicine* **40**, 1409–1422.

Navari S, Dazzan P (2009). Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychological Medicine* **39**, 1763–1777.

Noh JS, Kang HJ, Kim EY, Sohn S, Chung YK, Kim SU, Gwag BJ (2000). Haloperidol-induced neuronal apoptosis: role of p38 and c-Jun-NH_2-terminal protein kinase. *Journal of Neurochemistry* **75**, 2327–2334.

Parikh V, Khan MM, Mahadik SP (2003). Differential effects of antipsychotics on expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. *Journal of Psychiatric Research* **37**, 43–51.

Zhang XY, Tan YL, Cao LY, Wu GY, Xu Q, Shen Y, Zhou DF (2006). Antioxidant enzymes and lipid peroxidation in different forms of schizophrenia treated with typical and atypical antipsychotics. *Schizophrenia Research* **81**, 291–300.

Zipursky RB, Reilly TJ, Murray RM (2012). The myth of schizophrenia as a progressive brain disease. *Schizophrenia Bulletin*. Published online 7 December 2012. doi:10.1093/schbul/sbs135.

PHILLIP GRANT
Personality Psychology and Individual Differences, Justus-Liebig-University Giessen, Otto-Behaghel-Straße 10F, 35394 Giessen, Germany

(Email: phillip.grant@psychol.uni-giessen.de)