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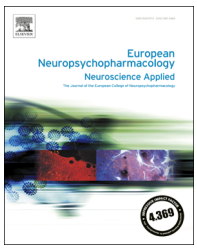

Transcriptomics and the mechanisms of antidepressant efficacy ☆

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Abstract
The mechanisms by which antidepressants have their effects are not clear and the reasons for variability in treatment outcomes are also unknown. However, there is evidence from candidate gene research that indicates gene expression changes may be involved in antidepressant action. In this study, we examined antidepressant-induced alterations in gene expression on a transcriptome-wide scale, exploring associations with treatment response. Blood samples were taken from a subset of depressed patients from the GENDEP study (n=136) before and after eight weeks of treatment with either escitalopram or nortriptyline. Transcriptomic data were obtained from these samples using Illumina HumanHT-12 v4 Expression BeadChip microarrays. When analysing individual genes, we observed that changes in the expression of two genes (*MMP28* and *KXD1*) were associated with better response to nortriptyline. Considering connectivity between genes, we identified modules of genes that were highly coexpressed. In the whole sample, changes in one of the ten identified coexpression modules showed significant correlation with treatment response (cor=0.27, p=0.0029). Using transcriptomic approaches, we have identified gene expression correlates of the therapeutic effects of antidepressants, highlighting possible molecular pathways involved in efficacious antidepressant treatment.

1. Introduction

Major depression is a leading cause of disease burden worldwide (Ustun et al. 2004), and is most commonly treated with antidepressants. There are a number of different antidepressant drugs with proven efficacy (Undurraga and Baldessarini 2012) and these are widely prescribed; for example over 50 million prescriptions were written for antidepressants in 2012 in England alone (HSCIC 2013). However, the molecular mechanisms that underlie the therapeutic action of these drugs remain unclear.

Antidepressants target monoaminergic systems, predominantly through the blockade of neurotransmitter transporters. But whilst this blockade occurs immediately after drug administration, there is often a significant delay of 2–3 weeks before the therapeutic effect of medications can be observed (Frazer and Benmansour 2002, Uher et al. 2011). This delay in treatment response may reflect the time needed for the biological changes that are required for treatment efficacy to occur. These biological changes are thought to involve changes in gene expression levels (Duman et al. 1997, Lesch and Schmitt 2002).

Using candidate gene approaches, gene expression alterations that are associated with treatment response have been observed within several key systems linked to antidepressant action; including inflammatory (Powell, Tansey et al. 2013), stress response (Cattaneo, Gennarelli et al. 2013) and neuroplasticity pathways (Belzeaux, Formisano-Treziny et al. 2010, Cattaneo, Bocchio-Chiavetto et al. 2010). By focusing specifically on those changes in gene expression that are associated with treatment outcomes, these studies are able to probe the mechanism by which these drugs exert their therapeutic effects (Gerhold, Jensen et al. 2002). This is particularly important in light of the high degree of variability seen between patients in terms of efficacy (Trivedi, Rush et al. 2006).

However, whilst many studies in patients have selected candidate genes of interest, by using microarray technology, it is possible to interrogate the entire transcriptome in a systematic and hypothesis-free manner. This enables the detection of novel gene expression changes which are associated with antidepressant efficacy, and places evidence regarding changes in expression levels for candidate genes within the context of the whole transcriptome (albeit it at the cost of a higher multiple-hypothesis testing burden, necessitating larger sample sizes). Indeed transcriptome-wide analyses using animal models indicate that gene expression changes associated with antidepressant action are likely to be complex, involving the co-ordinated change of many different transcripts to produce therapeutic effects (Sillaber, Panhuysen et al. 2008).

To date there are only a small number of studies exploring expression changes linked to treatment response in patients on a transcriptomic level. Using blood samples from 63 patients with major depressive disorder, Mamdani et al. (2011) identified 32 probesets that were differentially expressed according to response to citalopram, the most significant of which was Interferon Regulatory Factor 7 (*IRF7*). In contrast, Hennings et al (2015) used a discovery-replication design where they explored transcriptome-wide expression levels in 24 depressed patients (taking a range of antidepressants), and examined the top performing genes in a larger sample of 142 patients. In this manner, they observed that leucocyte-specific protein 1 (*LSP1*) significantly decreased in expression levels after 5 weeks of treatment in patients that responded or remitted to antidepressants (other genes associated with the prediction of treatment response were also identified but here we focus exclusively on antidepressant-linked change in gene expression, addressing the mechanism of drug action). Other studies that have looked at transcriptome-wide gene expression changes in patients receiving antidepressant