

Background and Hypothesis

Individuals with mood disorders exhibit altered function of the HPA axis in response to stress. The glucocorticoid receptor (GR) plays an important role in the negative feedback regulation of the HPA-axis. There are two protein isoforms of GR, GR α and GR β , which have distinct biological activity. Immune cells of depressed patients showed reduced response to dexamethasone (Calfa *et al.*, 2003) and are in a state of activation.

Hypothesis: The expression of GR α and GR β is aberrant in monocytes of SCZ and BD patients and expression levels correlate to the state of activation recently reported by us (R. Drexhage *et al.* 2010)

Results

Glucocorticoid receptor isoform expression in SCZ and BD

A	SCZ		BD	
	mean FC	p-Value	mean FC	p-Value
GR α	0.83	0.030	0.94	0.263
GR β	1.78	0.003	1.56	0.194

B	Gr β /GR α ratio		
	mean	St Dev	p-Value
SCZ	11.7	22.1	0.003
HC	3.6	4.4	
BD	1.6	0.9	
HC	1.1	0.5	

Figure 1
A) mRNA of 32/22 SCZ/BD patients and 34/22 age/gender matched controls (HC) was analyzed for GR α and GR β expression via qPCR and revealed down-regulated GR α (= active form) and up-regulated GR β (= inactive form) expression in SCZ and BD patients. B) GR α / β ratio calculation revealed that there's an increased ratio for in SCZ (over BD) indicating glucocorticoid resistance in the monocytes of these patients.

Inflammatory monocyte gene fingerprints in SCZ and BD

	Schizophrenia	Bipolar disorder		Schizophrenia	Bipolar disorder
Cluster 1A			Cluster 2		
DUSP2	5.36 <0.01	4.96 <0.01	hePTP	0.78 0.04	2.04 <0.01
ATF3	3.50 <0.01	3.55 <0.01	NAR2	0.76 0.21	2.58 <0.01
PDE4B	3.91 <0.01	3.00 <0.01	MAPK6	1.21 <0.01	1.80 <0.01
IL6	7.89 <0.01	5.39 <0.01	EMPI1	0.97 0.88	2.19 <0.01
IL1B	9.20 <0.01	6.45 <0.01	STX-1A	0.64 0.22	3.04 <0.01
TNF	3.91 <0.01	1.87 <0.01	DHRS3	1.08 0.51	1.87 0.08
TNFAIP3	3.22 <0.01	2.31 <0.01	CCL2	1.60 <0.01	3.83 <0.01
BCL2A1	2.39 <0.01	3.30 <0.01	CCL7	1.12 <0.01	8.47 <0.01
PTX3	2.51 <0.01	2.63 <0.01	CDC42	1.49 <0.01	1.99 <0.01
PTGS2	4.34 <0.01	3.20 <0.01	FABP5	1.08 0.75	1.21 0.09
CCL20	23.53 <0.01	10.63 <0.01	CD9	1.49 0.59	2.16 <0.01
CXCL2	3.76 <0.01	5.31 <0.01	HSPAL1A	1.06 0.93	0.79 0.40
EREG	7.36 <0.01	2.31 <0.01	CCR2	0.85 0.53	0.62 0.10
CXCL3	3.99 <0.01	3.33 <0.01			
Cluster 1B					
MXD1	1.49 <0.01	1.43 0.06			
F3	5.56 <0.01	1.87 0.02			
MAFF	5.10 <0.01	2.95 0.01			
EGR3	5.36 <0.01	2.52 0.16			
THBS	4.31 <0.01	2.02 0.05			
PAF-2	1.84 <0.01	1.10 0.06			
RGC32	0.85 0.07	2.61 <0.01			

Table 1
The quantitative value obtained from q-PCR is a cycle threshold (CT). The fold change values between different groups were determined from normalized CT values (CT gene-CT housekeeping gene), via the $\Delta\Delta CT$ method (User Bulletin, Applied Biosystems). The fold change of the HC was set to 1. Data are expressed relative to this HC value. HC SCZ: n=32; HC BD: n=48. Values >1: patients have a higher expression than control group. Boxes indicate significantly up-regulated. Values <1: patients have a lower expression than control group. Grey shaded box indicates significantly down-regulated. p-tested by univariate ANCOVA vs. control subjects; age and gender are included in this model.

GR α /GR β correlation analysis for SCZ, BD and healthy controls

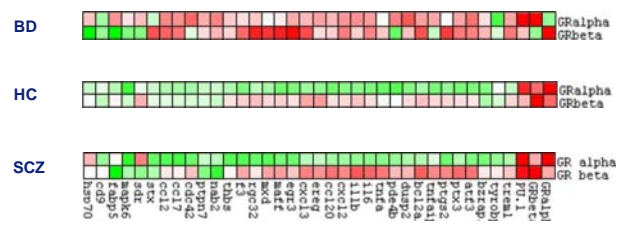
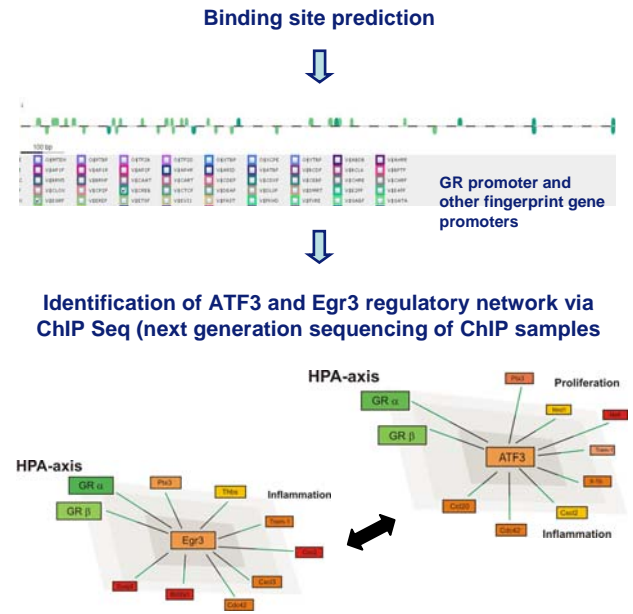


Figure 2
Spearman ranking revealed strong correlation between GR α and GR β expression in SCZ and BD patients and healthy controls (HC). GR α and GR β expression correlate strongly to the fingerprint genes in healthy controls but the correlation of GR α expression to the fingerprint genes is lost in both SCZ and BD patients' monocytes indicating that the aberrant expression of GR α and GR β coincides with the pro-inflammatory status of both SCZ and BD patient monocytes.

Outlook



Conclusions and Perspectives

1. GR α / β expression is reduced in monocytes of SCZ patients (and to a certain extent also in BD patients),
2. Up-regulated GR β expression correlates to the inflammatory gene expression found in the monocytes of SCZ patients.

New hypothesis: Since Egr3 and ATF3 are important transcription factors of the inflammatory signature (Weigelt *et al.*, submitted) analysis of transcriptional regulation by ATF3 and Egr3 of the GR promoter will unravel pathways relating pro-inflammatory monocyte activation to steroid resistance.