Peripheral glucocorticoid metabolism may reflect resolution of inflammation in Kawasaki disease

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Background

Kawasaki disease (KD) is an acute inflammatory disorder, associated with systemic vasculitis including coronary artery aneurysms (CAA). Treatment with intravenous immunoglobulin (IVIG) can resolve inflammation. However, about 20% patients show resistant to IVIG treatment and some of the cases required additional treatments. Recently, IVIG plus adjuvant glucocorticoid hormones (GC) has been shown to be an effective therapy for these patients, suggesting that GC may complement IVIG treatment in IVIG resistant-KD. We hypothesized that failure to appropriately regulate endogenous GC signaling may contribute to persistent inflammation in KD. Intracellular GC levels in peripheral tissues are controlled by pre-receptor metabolism by 11beta-hydroxysteroid dehydrogenase (11b-HSD). 11b-HSD1 converts intrinsically inert cortisone to active cortisol, increasing GC levels available to activate glucocorticoid receptor (GR).

Objective

The aim of this study was to establish if 11b-HSD1 in PBMC is associated with IVIG sensitivity in KD.

Methods

Levels of 11b-HSD1 and GR mRNA were measured in peripheral blood mononuclear cells (PBMC) isolated from all children diagnosed with KD at Teine-Keijinkai Hospital, Sapporo, Japan between April 2015 and January 2018 (a total of 31, table 1). IVIG was initiated in all patients on day 5 or 6 after the onset of high fever. Nineteen patients were classified as IVIG-sensitive patients, who showed complete resolution of high fever after initial IVIG treatment. Twelve patients were classified as IVIG-resistant due to persistent fever. Peripheral blood samples were obtained before and after IVIG treatment with informed consent. RNA was extracted from PBMC. 11b-HSD1 and GR mRNA levels were measured by qRT-PCR.

Table 1. Summary of KD patient characteristics

N =31		IVIG-sensitive (n=19)		IVIG-resistant (n=12)	*P* (sensitive vs. resistant)
Age (years), mean (range)		2.89 (0.7-6.1)		3.07 (1.3-5.2)	0.715
Gender (%)	Boys	53%		50%	0.8864
	Girls	47%		50%	
Body temperature (°C), mean ± S.E.M.					
	before IVIG	39.57 ± 0.13		39.68 ± 0.21	0.7141
	after IVIG	36.78 ± 0.08		38.86 ± 0.25	**< 0.0001**
Laboratory data, mean ± S.E.M.					
WBC (per mm^3)	before IVIG	12986 ± 820		15073 ± 1124	0.0777
	after IVIG	6415 ± 570		10324 ± 1138	**0.0057**
CRP (mg/dl)	before IVIG	8.71 ± 1.27		9.72 ± 1.55	0.5034
	after IVIG	2.56 ± 0.63		5.03 ± 1.70	0.2068
mRNA levels, mean ± S.E.M.					
11β-HSD1 mRNA	before IVIG	1.849 ± 0.392	***p* = 0.0386**	1.749 ± 0.765	0.5039
	after IVIG	**4.330 ± 1.146**		1.361 ± 0.237	0.3307
GR mRNA	before IVIG	5.679 ± 0.870		3.860 ± 0.497	0.1246
	after IVIG	7.423 ± 1.847		4.336 ± 0.613	0.4548

Results

There was no significant difference in the basal levels of 11b-HSD1 and GR mRNA between IVIG-sensitive and –resistant KD (Table 1). However, following IVIG treatment, 11b-HSD1 mRNA levels were significantly increased in IVIG-sensitive KD, but not in IVIG-resistant KD. There was no significant effect of IVIG treatment on GR mRNA levels in either group.

Conclusion

Increased 11b-HSD1 activity in PBMC is predicted to increase the intracellular levels of cortisol generated from cortisone, thereby amplifying intracellular GC-mediated attenuation of proinflammatory cytokine action in PBMC of IVIG-sensitive KD. In contrast, the failure to up-regulate 11b-HSD1 in PBMC in IVIG-resistant KD patients might contribute to the persistence of inflammation. Understanding the role of endogenous glucocorticoid signaling in immune cells during the course of KD may highlight future possible therapeutic avenues to treat IVIG-resistant KD.

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