Opioid Use, Gene Expression and Gene Variants Involved in Pain, Inflammation and Dependency Pathways

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Background/Introduction: Opioid consumption may influence gene expression of proteins associated with pain transmission and inflammation. With the development of mRNA sequencing tools, investigators have measured gene expression of proteins involved in pain transmission. One aim of this preliminary study was to compare mRNA expression of proteins in opioid consuming and opioid naïve patients before and after surgery. We focused on genes that might alter microglia activation. Recent work has implicated opioids as an activator of microglial cells via an increase in the expression of pro-inflammatory cytokines and components of the complement cascade. Our hypothesis was that gene expression of selected complement cascade proteins would be different in these patient groups before and/or 24 hours after surgery for lower extremity total joint replacement.

Gene variants may also contribute to how patients experience perioperative pain. A second aim was to explore differences in single nucleotide polymorphisms (SNPs) of genes in drug metabolism, GABA, and prostaglandin pathways between opioid naïve and consuming patients. Only those SNPs with moderate to deleterious impact were considered. Our hypothesis was that opioid consuming patients would have more SNPs than opioid naïve patients.

Methods: In a convenience sample of 20 patients undergoing elective lower extremity total joint replacement, ASA class I-III, with 48+ hour hospital stay, we compared genes associated with pain and inflammation in patients that consumed opioids (3-120 mg of oral morphine equivalents per day, n= 11) to those that did not (n=9) for differential expression. WBCs were assayed for mRNA expression of complement proteins and gene variants in drug metabolism, GABA, and prostaglandin pathways.

Results: The gene expression of a complement inhibitor, C4BPA, was reduced and the expression of a complement activator, CFD, was increased in opioid consuming patients (Figure 1). Gene variants in drug metabolism, GABA, and prostaglandin pathways were more common in opioid consumers (average number of variants = 2.45) than in opioid naive patients (average number of variants = 0.67, Table 1).

Conclusions: This preliminary work suggest opioid consuming patients may have genetic susceptibility to altered pain and inflammatory responses and altered expression of inflammation pathways. Additional work is warranted to confirm these findings.

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Figure 1

Figure 1A **Figure 1B**

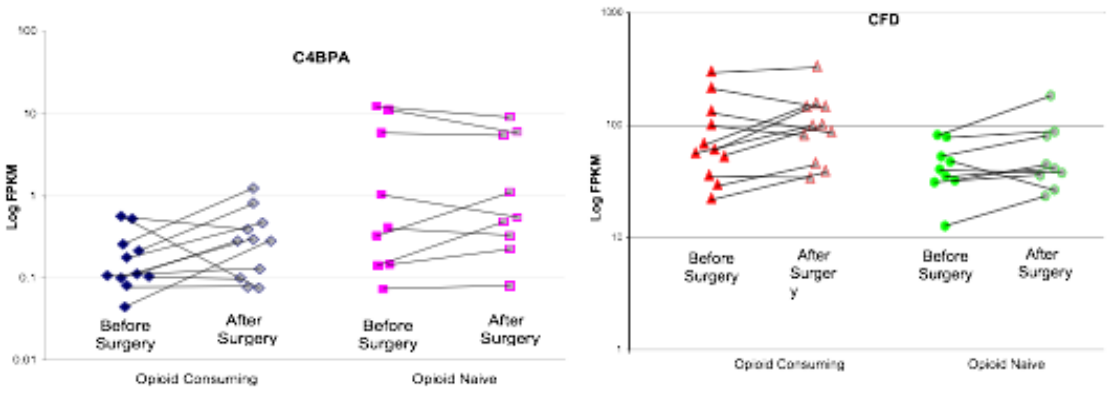

Figure 1. White blood cell messenger RNA Fragments Per Kilobase Million mapped reads (FPKM) for Complement 4 Binding Protein (C4BPA) in opioid consuming (diamonds) and opioid naïve patients (squares, Figure 1A) and FPKM for Complement Factor D (CFD) in opioid consuming (triangles) and opioid naïve patients (circles, Figure 1B) before and 24 hours after surgery. In RNA-Seq, the relative expression of a transcript is proportional to the number of cDNA fragments that originate from it. Data are from each of the 20 individual patients. The before and after surgery values for the same patient are linked (black lines). FPKM values are presented on a log scale (base 10).

Table 1. Gene Variants in Opioid Naïve and Consuming Patients

Opioid Consuming Patients (n=11, mean number of variants= 2.45)

ID	Drug Metabolism Variants			Prostaglandin Variants		GABA Variants	Total
1							0 variants
4	CYP1B1			PTGES2			2 variants
8	CYP1B1			PTGES2		DBI	3 variants
10	CYP1B1						1 variant
12	CYP1B1			PTGES2	PTGS1		3 variants
13	CYP1B1				PTGS1		2 variants
14	CYP1B1			PTGES2			2 variants
15	CYP1B1	AHR	AKR1A1			DBI	4 variants
16	CYP1B1	AHR	AKR1A1				3 variants
17	CYP1B1			PTGES2		DBI	3 variants
19	CYP1B1	AHR	AKR1A1		PTGS1		4 variants

Opioid Naive Patients (n=9, mean number of variants= 0.67)

2							0 variant
3				PTGES2			1 variant
5	CYP1B1		AKR1A1				2 variants
6							0 variant
7	CYP1B1						1 variant
9							0 variant
11							0 variant
18	CYP1B1						1 variant
20	CYP1B1						1 variant

CYP1B1: Cytochrome P450 Family 1 Subfamily B Member 1, monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids.
AHR: Aryl Hydrocarbon Receptor, regulates metabolizing enzymes such as cytochrome P450.
AKR1A1: Aldo-Keto Reductase Family 1 Member A1, participates in both the drug metabolism and prostaglandin pathways.
PTGES2: Prostaglandin E Synthase 2, catalyzes the conversion of prostaglandin H2 to prostaglandin E2
PTGES1: Prostaglandin-Endoperoxide Synthase 1, catalyzes the conversion of arachinodate to prostaglandin.
DBI: Diazepam Binding Inhibitor, involved in lipid metabolism and the displacement of beta-carbolines and benzodiazepines, which modulate signal transduction at type A gamma-aminobutyric acid receptors located in brain synapses.
Source: https://www.genecards.org/