Occupancy of Naltrexone at Kappa Opioid Receptors may Predict Efficacy in Reducing Drinking in Alcoholics

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INTRODUCTION

Naltrexone (NTX) is a non-selective opioid antagonist that has been shown to have variable efficacy in treating alcohol addiction. It is known that an individual’s family history of alcoholism is a predictor of positive response to NTX (Krishnan-Sarin et al., 2007). Naltrexone’s efficacy may be related to binding to three types of opioid receptors – mu, kappa, or delta. It has been shown that at a dose of 50 mg/day, NTX causes almost complete occupancy of the mu-opioid receptors in the brain (Weerts et al., 2008), suggesting that any differential efficacy of NTX between groups could be due to binding at other receptor sites. The current project is the first imaging study to examine the importance of kappa opioid receptors (KOR) and NTX in human, alcohol dependent, heavy drinkers with a positive and negative family history of alcoholism.

Positron Emission Tomography (PET) imaging and a new KOR-antagonist tracer, 11C-LY2975050 (Zheng et al., submitted) (see SJ Kim et al poster no. P115 for selectivity data), were used to determine the occupancy of the KORs in the brain before and after treatment. An Alcohol Drinking Paradigm (ADP) was used to quantify reduction in drinking. It was seen, preliminarily (n=6), that low occupancy of KOR by NTX may be associated with poor efficacy of treatment – and with absence of family history of alcoholism. Family history negative alcoholics experienced less reduction in craving (4.6±.6 vs. 10.2±.60 on Yale Craving Scale) and less reduction in drinking (2.5±.12 vs 5±.94 drop in drinks from 1st to 2nd ADP) following NTX treatment than those with a positive family history.

METHODS

Protocol

Intake & PE MRI

Day 1

PE

Day 2

Day 3

50 mg

Day 4

100 mg

Day 11

2nd PET

Follow-Up

Medication (daily visits)

Endpoints

1. LY2975050 total volume of distribution (Vt) was estimated using the 2TC Model
2. Occupancy was calculated via the Lassen Plot Method
3. Efficacy of NTX was determined by reduction in drinks from first to second ADP
4. Craving was measured with the Yale Craving Scale

Subjects

1. Male
2. Physically and mentally healthy
3. Met NIAAA Criteria for Hazardous Drinking
4. Not seeking treatment for alcoholism
5. Did not meet abuse or dependence criteria for other substances

RESULTS

Figure 2. Baseline drinking and baseline Vt in top four regions of tracer uptake.

Figure 3. Pre- and post-NTX SUV 0-120 min. emission images in one FH+ and one FH- subject. Note greater occupancy of NTX in FH+ subject as determined by lower uptake of tracer post-drug.

Figure 4. Grouping of subjects by NTX occupancy (<80% vs >80%). High Occupancy group cravings reduced more than Low Occupancy group after week of NTX treatment. (Note overlap of points in High Occupancy group post-NTX)

Figure 5. Grouping of subjects by NTX occupancy (<80% vs >80%). High Occupancy group reduced their drinking more than Low Occupancy group after week of NTX treatment. (Note overlap of points in High Occupancy group post-NTX)

CONCLUSIONS

High occupancy of naltrexone at kappa opioid receptors and family history of alcoholism appear (preliminarily) to be associated with reduced efficacy in craving for alcohol and with reduction in drinking.

REFERENCES


Table 1. Subjects’ demographic information

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1. Evan Morris, Su Jin Kim, Nicholas Franco, Dana Cavallo, Alisha Jordan, Julia Gillard, Ming-Qiang Zheng, Shu Fei Lin, Yiyun Huang, Suchitra Krishnan-Sarin.