Journal of Alcoholism & Drug Dependence

Hiranita, J Alcohol Drug Depend 2016, 4:6
DOI: 10.4172/2329-6488.1000e135

Editorial Open Access

Lack of Effects of Toll-Like Receptor 4 Antagonists on the Reinforcing Effects of Cocaine and Remifentanil

Takato Hiranita*

Division of Neurotoxicology, National Center for Toxicological Research (NCTR), U.S. Food and Drug Administration (FDA), AR 72079-9501, USA

***Corresponding author:** Hiranita T, Division of Neurotoxicology, National Center for Toxicological Research (NCTR), U.S. Food and Drug Administration (FDA), 3900 NCTR Road, Jefferson, AR 72079-9501, USA, Tel: 870-543-6823; Fax: 870-543-7745; E-mail: takato.hiranita@fda.hhs.gov

Received date: November 18, 2016; **Accepted date:** November 18, 2016; **Published date:** November 25, 2016

Editorial

The toll like receptor 4 (TLR4) is expressed in glial cells and reacts to potential toxic entities. This activation triggers various inflammatory reactions. (+)-Naloxone and (+)-naltrexone, dextrorotatory enantiomers of opioid receptor antagonists [respectively, (-)-naloxone and (-)-naltrexone], have been demonstrated to dock to TLR4 using "*in-silico*" models, and function as an antagonist at this site *in vivo* [1,2]. Recently, (+)-naloxone have been reported to antagonize self-administration of a μ-opioid agonist remifentanil [3]. Further, (+)-naltrexone blocked self-administration of a dopamine uptake inhibitor cocaine [4]. These findings suggested a "novel" TLR4-mediated mechanism underlying the reinforcing effects of drugs of abuse across pharmacological classes. A more recent study [5] has, however, indicated that the TLR4 hypothesis is less viable.

Tanda and his colleagues further assessed specificity of the blocking effects of the TLR4 antagonists on self-administration of remifentanil or cocaine [5]. Consistent with the results from the two earlier studies [3,4], both (+)-naloxone and (+)-naltrexone dose-dependently produced an insurmountable antagonism against self-administration of remifentanil or cocaine. However, the antagonism was accompanied with a dose-dependent decrease in food-reinforced responding. For example, (+)-naloxone and (+)-naltrexone were equipotent in decreasing responding maintained by injections of remifentanil or cocaine or presentations of food pellets. Thus, the apparent antagonism of the TLR4 antagonists against drug self-administration is likely due to a non-specific disruption of overall behavioral performance rather than an interaction with the reinforcing effects of cocaine or remifentanil. On the other hand, cocaine was not reinforcing under a fixed- and progressive-ratio schedule of reinforcement in TLR4 mutant mice whereas sucrose was reinforcing [4]. Thus, TLR4 signaling appears to mediate somehow cocaine reinforcement.

The more recent results by Tanda et al. [5] indicate the following message: 1) There is no specific preclinical efficacy of TLR4 antagonists (+)-naloxone and (+)-naltrexone for self-administration of cocaine and remifentanil. Thus, the TLR4 hypothesis is less viable to develop medications for drug abuse; 2) It is important to assess pharmacological specificity using food-reinforced responding as successfully employed in previous studies [5-9].

Acknowledgments

The present work was supported by the Division of Neurotoxicology/NCTR/U.S. FDA (Dr. Merle G. Paule). The information in this article is not a formal dissemination of information by the FDA and does not represent agency position or policy. The author thanks Drs. Merle G. Paule and Matthew Bryant at NCTR for comments during the preparation of the manuscript.

References

1. Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, et al. (2008) Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). Eur J Neurosci 28: 20-29.
2. Lewis SS, Loram LC, Hutchinson MR, Li CM, Zhang Y, et al. (2012) (+)-naloxone, an opioid-inactive toll-like receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats. J Pain 13: 498-506.
3. Hutchinson MR, Northcutt AL, Hiranita T, Wang X, Lewis SS, et al. (2012) Opioid activation of toll-like receptor 4 contributes to drug reinforcement. J Neurosci 32: 11187-11200.
4. Northcutt AL, Hutchinson MR, Wang X, Baratta MV, Hiranita T, et al. (2015) DAT isn't all that: cocaine reward and reinforcement require Toll-like receptor 4 signaling. Mol Psychiat 20: 1525-1537.
5. Tanda G, Mereu M, Hiranita T, Quarterman JC, Coggiano M, et al. (2016) Lack of Specific Involvement of (+)-Naloxone and (+)-Naltrexone on the Reinforcing and Neurochemical Effects of Cocaine and Opioids. Neuropsychopharmacology 41: 2772-2781.
6. Hiranita T, Wilkinson DS, Hong WC, Zou MF, Kopajtic TA, et al. (2014) 2-isoxazol-3-phenyltropane derivatives of cocaine: molecular and atypical system effects at the dopamine transporter. J Pharmacol Exp Ther 349: 297-309.
7. Li L, Hiranita T, Hayashi S, Newman AH, Katz JL, et al. (2013) The stereotypy-inducing effects of N-substituted benztropine analogs alone and in combination with cocaine do not account for their blockade of cocaine self-administration. Psychopharmacology 225: 733-742.
8. Hiranita T, Soto PL, Kohut SJ, Kopajtic T, Cao J, et al. (2011) Decreases in cocaine self-administration with dual inhibition of the dopamine transporter and sigma receptors. J Pharmacol Exp Ther 339: 662-677.
9. Hiranita T, Soto PL, Newman AH, Katz JL (2009) et al. Assessment of reinforcing effects of benztropine analogs and their effects on cocaine self-administration in rats: comparisons with monoamine uptake inhibitors. J Pharmacol Exp Ther 329: 677-686.