Tuhin Suvro Banerjee et al., Brain Disord Ther 2015, 4:5
http://dx.doi.org/10.4172/2168-975X.S1.006

OMICS International
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International Conference on
Brain Disorders & Therapeutics
August 24-26, 2015 London, UK

Anti addictive role of 2-(2-methylquinolin-4-ylamino)-N-phenyl acetamide in epigenetic regulation in alcohol addiction

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Very few pharmacological treatments exist for treatment of chronic alcoholism. Both aversive and non-aversive therapies with Disulfiram and Acamprosate respectively have their limitations and produce side effects. Naltrexoneapproved in 1994 as a non-aversive drug was found to be associated with dose-dependent hepatotoxic side effects. Previous studies from this laboratory had identified aquinoline compound S4 [C18H17N3O; 2-(2-methylquinolin-4-ylamino)-N-phenyl acetamide] which could successfully inhibit withdrawal symptoms in mice rendered dependent on morphine. It was observed that S4 had dual affinity for μ and κ opioid receptors. In the present study we investigated whether S4 could also attenuate alcohol seeking behavior in alcohol dependent mice. It was found that pretreatment with S4 significantly reduced the alcohol intake in the addicted animal in a dose dependent manner and inhibited the body weight loss during the withdrawal period. Drug-induced alterations in chromatin structure may contribute to long-lasting behavioral changes in addicts and may provide a novel therapeutic approach for improving drug rehabilitation. We observed significant alteration in histone trimethylation and dimethylation at Lys9 in alcohol seeking animals compared to alcohol abhorring mice. The histone modifying enzyme, JMJD2A which converts trimethylated histone to dimethylated histone was significantly altered in the alcohol seeking animals which could account for the observed differences in the histone trimethylation levels in the two groups. The effect of S4 on the above parameters in the alcohol seeking mice was also investigated. Attempts have also been made to identify the epigenetic signatures for alcohol addiction by studying the phosphorylation and acetylation patterns of histone H3 in the two groups and the effect of S4 in order to understand the mechanism of action of this novel anti-addictive compound.

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