SECTION 8:

SUMMARY AND CONCLUSION

Candidate: Ashish Kumar Rehni
The present study has been designed to investigate the effect of SU-6656; ammonium pyrrolidine dithiocarbamate (APD); RS 102895; tributyrin; trichostatin A; N-Acetyl-Asp-Glu-Val-Asp-al; Sodium orthovanadate or SJA 7019 on the development of morphine withdrawal syndrome both in vivo in mice and in vitro in morphine withdrawn rat ileum preparation. The present study further explored the possibility of a potential synergistic interaction between APD and RS 102895 as well as trichostatin A and N-Acetyl-Asp-Glu-Val-Asp-al using an isobolographic study design and analysis. Sub-acute morphine administration followed by a single injection of naloxone (8 mg/kg, i.p.) was used to precipitate opioid withdrawal syndrome in mice. Behavioral observations were made immediately after naloxone treatment. Withdrawal syndrome was quantitatively assessed in terms of withdrawal severity score and frequency of jumping, rearing, fore paw licking & circling. Separately naloxone induced contraction in morphine dependent isolated rat ileum was employed as an in vitro model.

On the basis of results obtained in the present study, the following salient findings may be summarized.

1. Administration of morphine (5mg/kg, i.p.) twice daily for a period of 5 days followed by a single injection of naloxone (8mg/kg, i.p.) precipitated withdrawal syndrome in mice as reflected by a significant increase in stereotyped jumping behavior, withdrawal severity score, rearing activity, fore paw licking behavior and circling behavior in morphine/ naloxone group, when compared to that of the vehicle treated control groups.

2. Co administration of SU6656 or APD or RS 102895 or tributyrin or trichostatin A or Ac-DEVD-CHO or sodium orthovanadate or SJA 7019 significantly and dose dependently attenuated naloxone induced withdrawal syndrome in morphine dependent mice.
3. Naloxone challenge immediately followed a brief period of 4 minutes morphine exposure, elicited a strong contracture in the rat ileum preparation in terms of the tension ratio results.

4. Administration of SU6656 or APD or RS 102895 or tributyrin or trichostatin A or sodium orthovanadate or SJA 7019 significantly and dose dependently attenuated this naloxone induced withdrawal response in morphine dependent rat ileum preparation.

5. The isobolographic analysis of the combination of APD and RS 102895 showed the presence of a synergistic interaction between APD and RS 102895.


7. It may be concluded that the inhibition of src-kinase; histone deacetylase; interleukin-1-β converting enzyme; nuclear factor kappa B; chemokine CCR-2 receptor; tyrosine phosphatase and calpain attenuates the development of morphine dependence as observed in the naloxone-induced precipitation of withdrawal symptoms in morphine dependent mice. Therefore, inhibitors of these targets may be considered as novel pharmacological interventions for the management of morphine (opioid) withdrawal syndrome.