



P.6.c.014. ACTH4-10 analogue *Semax* and Adamantane derivative *Hemantane* produce significant reduction of withdrawal signs in morphine-dependent rats

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Introduction:

The mechanism of opioid-like addiction has defined connections with DA-ergic reward system as well as with glutamate and NMDA systems of the brain. At the same time, some neuropeptides, namely, CCK analogues and one of taftsin derivatives, are able to reduce the severity of withdrawal signs in morphine-dependent rats [1,2] that give as the opportunity to suggest the modulating effect of these peptides in relation to opioid induced addiction. These facts have been considered when searching for new compounds with different action mechanisms to prevent and relieve the state of dependence. The main effects of **Semax** are its nootropic, neuroprotective and anxiolytic activity with the participation of serotonergic and CCK-receptors and, possible, BDNF [3], while **Hemantane** and **Adamantane** have an well-marked antiparkinsonian activity with the involvement of glutamatergic and NMDA receptor mechanisms [4].

Aim The present study was started to investigate the effects of the adrenocorticotrophic hormone fragment, ACTH4-10, heptapeptide **Semax** (Inst. of Mol. Genetics RAN, Moscow) in comparison with those of **Hemantane** (N-adamant-2-yl-hexamethyleneimine hydrochloride, V.V. Zakusov Inst. of Pharmacology, Moscow) and **Amantadine hydrochloride** (1-aminoadamantane hydrochloride, *Sigma-Aldrich*), as a reference drug, upon opiate withdrawal syndrome (WS), tactile thresholds in “von Frey test”(Ugo Basile) and ambulation in the “open field”(OF)

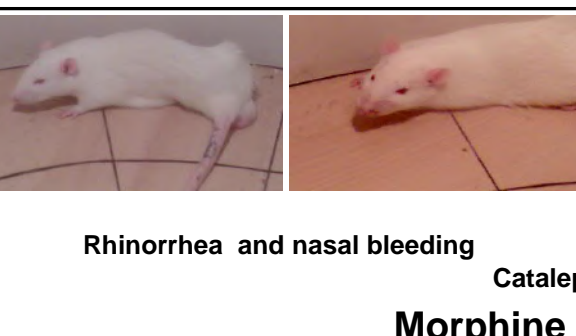
Methods Incremental doses of morphine were injected i.p. to outbred male rats for 5 days followed by **Naloxone** (*Du Pont De Nemours*), 1mg/kg, to provoke acute WS. Peptide **Semax** (0.05 – 0.5 mg/kg), **Hemantane** (10 – 20 mg/kg), **Amantadine** (10 - 20 mg/kg) have been injected one fold, 45 min before the test started in the “open field” or daily, 30 min before the morphine injections; 16 behavioural, neurological and vegetative signs of WS were registered in rats, placed in OF, after that the Total Index (TI) of WS was evaluated [5]. Plantar tactile thresholds were measured via “von Frey” test (*Ugo Basile*) before the beginning of morphine injections and after morphine withdrawal. The BW changes were marked every second day. For statistical assay Mann-Whitney-test, one way ANOVA and were used.



Flattening pose, ptosis, tonic seizures and writhing



Rhinorrhea and nasal bleeding



Catalepsy

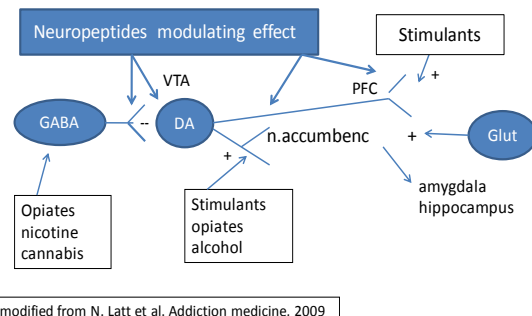


Tail flick & Hot plate Tests

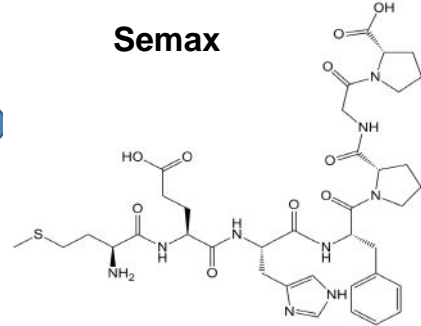
Morphine acute effects

Signs of morphine withdrawal syndrome

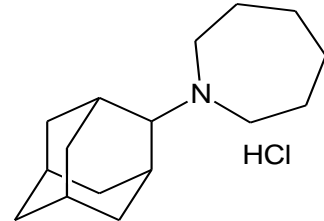
«DA-related conception of addiction with possible neuropeptides involvement



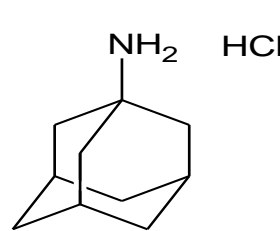
modified from N. Latt et al. Addiction medicine, 2009



Hemantane



Amantadine



A way to addiction...



Von Frey test (tactile sensitivity test)

SUMMARY OF RESULTS

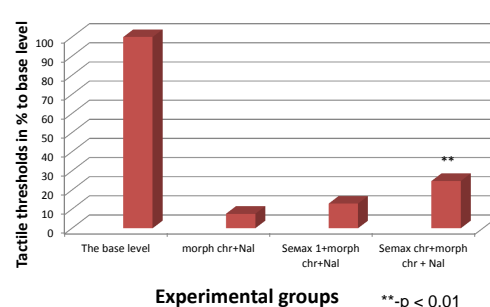
Semax, administered in a small single doses of 0.05 mg/kg eliminated individual features and decreased TI of morphine WS by 36.4%, $p < 0.05$. Subchronic administration of morphine with **Semax** in same dose decreased the TI of WS by 30.0 %, $p < 0.05$. The higher doses of **Semax** (0.5 mg/kg) were not effective in relation to TI of WS. The tactile thresholds were restored significantly to the 24.7% level followed by **Semax** was given subchronically in small dose (0.05 mg/kg) to morphine-dependent rats, comparing with “morphine + naloxone” group level of 7.59 % ($p < 0.009$).

Hemantane administered once in single doses of 10 and 20 mg / kg, significantly reduced the severity of TI of WS, respectively by 46% and 33.2% and induced the decrease in severity or elimination of such signs of WS as vocalization, teeth chattering and ptosis. **Amantadine** did not exert statistically significant effect on the indices of morphine WS. Moreover, it caused a number of negative side effects, namely, a decrease of locomotion and tactile thresholds, an additional BW drop and induced the aggressive behaviour in abstinent morphine dependent rats.

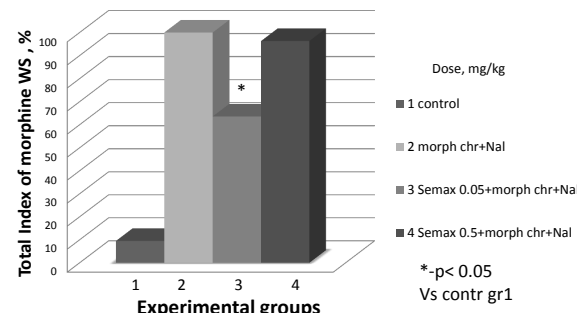
CONCLUSION

ACTH4-10 analogue, heptapeptide **Semax** and N-adamantane derivative **Hemantane**, but not **Amantadine**, are promising preparations for correction of opioid addiction. **Amantadine** had not influence on any signs of morphine withdrawal syndrome in rats and demonstrated additional side effects in these animals.

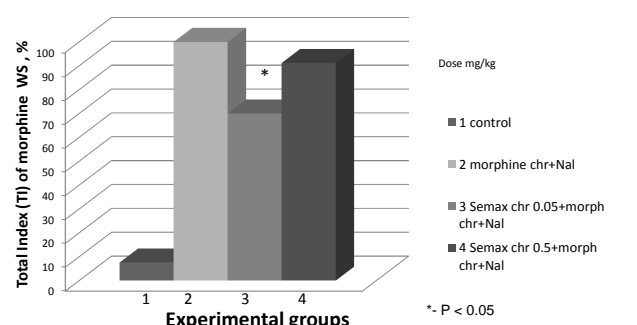
The influence of Semax on tactile thresholds in morphine-dependent rats after a single or chronic application



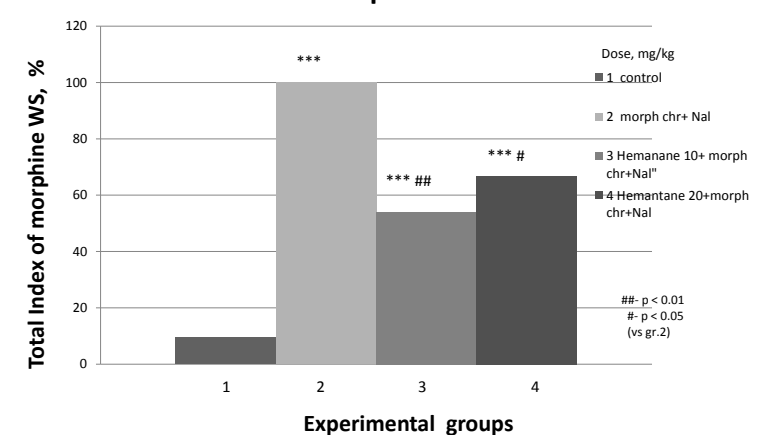
Effect of Semax applied in a single i/p doses upon morphine WS in rats



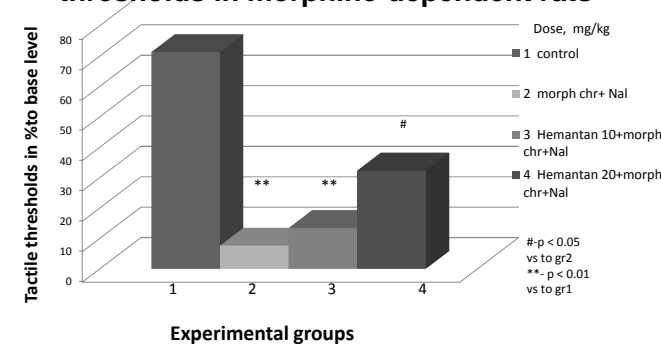
Effect of chronic Semax administration upon opiate WS in male rats



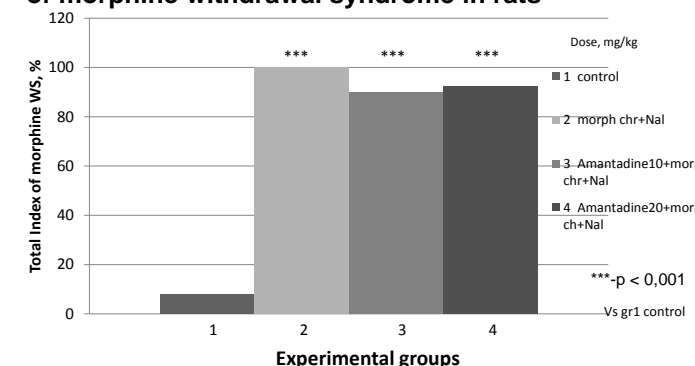
The influence of Hemantane on behavioural indices of morphine WS in rats



The effect of Hemantane upon tactile thresholds in morphine-dependent rats



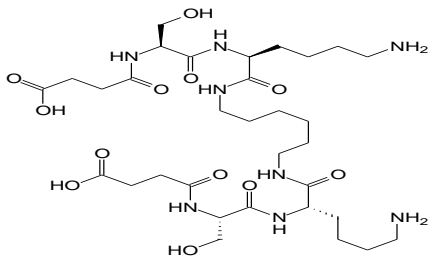
Amantadine can not eliminate the behavioral symptoms of morphine withdrawal syndrome in rats



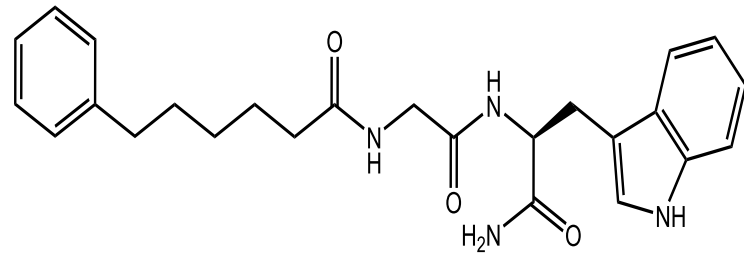
References

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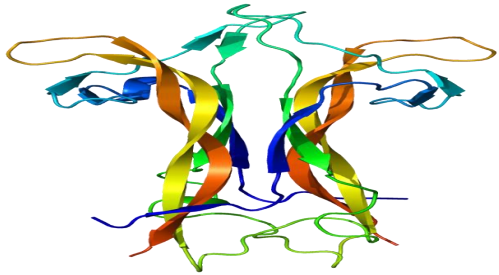
Disclosure statement : there is not potential conflict of interest .



Dipeptide mimetic of BDNF GSB-106



GB-115 $\text{Ph}(\text{CH}_2)_5\text{CO-Gly-Trp-NH}_2$



THE BDNF CONFORMATION

