Mixed Sigma-1 / Sigma-2 ligands as analgesics: studies with ANAVEX 1066 in animal models of neuropathic pain and visceral pain

J. Sprouse[1], N. Rebowe[1], Y. Darbaky[2], L. Diop[2], D. Klamer[1] and C. Missling[1]

[1]Anavex Life Sciences Corp., New York, USA, [2]ANS Biotech, Riom, FRANCE

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Background

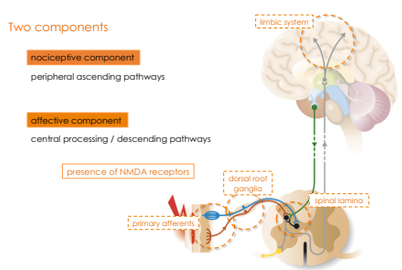
ANAVEX 1066

Safe and effective therapeutics acting on novel molecular targets are actively being investigated for pain management due to the limitations associated with currently marketed interventions. ANAVEX 1066, a mixed Sigma-1 / Sigma-2 receptor ligand, has previously demonstrated antitumor activity as well as analgesic effects in animal models (Riganas et al., 2012).

The present work extends this latter finding to an additional model of neuropathic pain, the chronic constriction injury model, and to a model of visceral pain as induced by the inflammatory agent trinitrobenzene sulfonic acid (TNBS).

Sigma Receptors and the Link to Pain

The precise mechanism of action for the analgesia produced by mixed Sigma-1/Sigma-2 receptor ligands is in the process of being further elucidated. Currently, converging evidence suggests that the mechanism may involve a modulatory action on NMDA receptors (Kim et al., 2008), a subtype of glutamate receptor known to transmit pain information.

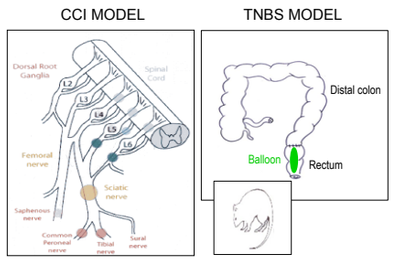


As illustrated above, there are NMDA receptors situated at multiple sites along the pain pathways, both in terms of the nociceptive component that ascends from the periphery and the affective component that originates centrally and informs processing along the spinal cord.

Experimental Procedures

Chronic Constriction Injury (CCI) Model of Neuropathic Pain

The CCI model (Bennett & Xie, 1988) consisted of a loose ligation of the sciatic nerve performed under anesthesia with the development of a peripheral mono-neuropathy as assessed 14 days post-operative. Testing of the ipsalateral paw revealed a reduction in the pressure required to elicit paw withdrawal compared to the healthy contralateral paw. Morphine served as the positive control.



TNBS Model of Chronic Visceral Pain

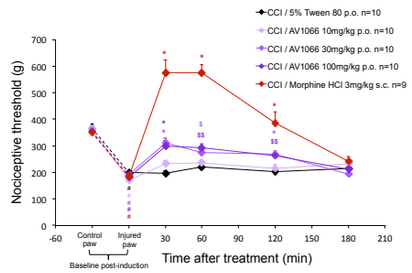
Hypersensitivity was induced by direct injection of the inflammatory agent into the proximal colon (50 mg/kg) 7 days prior to testing (Diop et al., 2002). Inflation of a balloon inserted into the rectum produced a colo-rectal distension and in turn a greater sensitivity vs. sham animals as noted by characteristic changes in posture (inset). U50-488H, a kappa opioid receptor agonist, served as the positive control.

Intestinal transit was assessed post mortem by the movement of the charcoal front following oral administration of a suspension (Harrison et al., 2012). A slowing of transit may be indicative of a constipating effect of the drug and in light of this morphine served as the positive control.

The **Modified Irwin Grid** consisted of a series of 45 distinct behavioral signs selected to capture general safety and tolerability.

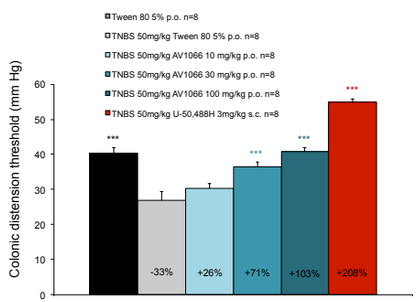
Statistics for all studies began with an ANOVA and (if significant) were followed by post hoc multiple comparison tests.

AV1066 Significantly Reduces Neuropathic Pain



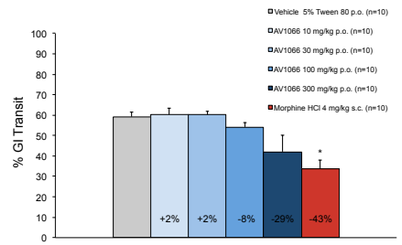
- Nociceptive threshold was significantly lower in the injured paw vs. the control paw (#, $p < 0.001$) indicating a degree of mechanical hypersensitivity and hence a mononeuropathy.
- AV1066 reduced this hypersensitivity in a dose-dependent fashion (*, $p < 0.05$ vs. vehicle group; $, $$, $p < 0.05$, 0.01 vs. vehicle group). Morphine increased the nociceptive threshold in both the injured and healthy paws (see Discussion).

AV1066 Significantly Reduces Visceral Pain



- Injection of TNBS into the proximal colon produced a chronic hypersensitivity based on the decrease in balloon inflation pressure required to produce a postural change 7 days post surgery in treated vs. vehicle-injected animals.
- AV1066 produced a dose-dependent increase in the colonic distension threshold, returning this value of hypersensitivity to normal levels (***, $p < 0.001$ vs. vehicle group). U-50,488H typically increases colonic distension threshold even in vehicle-treated animals (data not shown).

AV1066 Demonstrates Low Risk of Constipation



- No significant effect of AV1066 was observed on charcoal transit; as expected, morphine produced a significant decrease (*, $p < 0.05$), an effect consistent with the capacity of this compound to produce constipation in patients.
- As such, AV1066 appears to be free of transit issues at doses that exceed those required to restore colonic distention threshold.

AV1066 Demonstrates a Favorable Safety Profile in the Irwin Grid

Rectal temperature	Writhing	Abnormal behavior	Salivation
General arousal	Ptosis	Grooming	Heart rate
Eating	Pupil diameter	Fear	Respiration
Drinking	Exophthalmos	Locomotion	Color
Aggression	Grasping	Gait	Tail sensitivity
Vocalization	Chromo-dacryorrhea	Rearing	Noise response
Arousal	Lacrimation	Sudden start	Corneal reflex
Catalepsy	Defecation	Staggered gait	Convulsions
Passivity	Feces consistency	Posture	Tremor
Tactility	Urination	Body tone	Stereotypy
Tremor	Urine color	Muscle tone	Tremor
Tactility	Piloerection	Tail position	

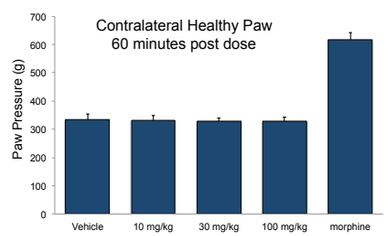
- Of the 45 behavioral signs that were measured in the Modified Irwin Grid, only a small effect was observed on muscle tone and grasping up to a dose of 1000 mg/kg p.o. (N = 5 per dose group).
- Compared to the dose range that produced efficacy in the CCI model of neuropathic pain and the TNBS model of visceral pain, AV1066 appears to possess a favorable safety profile.

Discussion

The mixed Sigma-1/Sigma-2 ligand AV1066 appears to be an intriguing possibility for use in both neuropathic and visceral pain based on the following observations from the current studies:

- AV1066 produced a dose-dependent reversal of the hypersensitivity that develops in animal models of both neuropathic and visceral pain.
- The reversal of the hypersensitivity with AV1066 appeared to be complete as drug-treated levels and vehicle-treated / sham levels were indistinguishable.
- AV1066 had no significant effect on the rate of intestinal transit, a surrogate marker for constipation, at doses in which it relieved visceral pain, and demonstrated only a limited effect in the Irwin Grid, a behavioral battery commonly used in estimating general safety and toleration.

In the CCI model of neuropathic pain, AV1066 did not impact nociception in the contralateral healthy paw in contrast to morphine, which has an analgesic effect in both paws. This suggests that AV1066 acts in a state-selective manner and only impacts nociception during periods of patho-physiological stress.



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