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(1) Promises and Pitfalls of Peripheral Opiate Analgesia Research

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(2) Opioid Peptide Analogues as a Potentially New Generation of Analgesics

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PROMISES AND PITFALLS OF PERIPHERAL OPIATE ANALGESIA RESEARCH

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THE PROMISE: Because of the widespread impact on the central nervous system of both pain impulses and opiate analgesics, it has been assumed that a peripheral opiate analgesic action would be of great clinical value. Unfortunately both the basic science and clinical studies conducted to date have not provided evidence that would suggest that such peripheral actions will be of great clinical importance. While even the earliest of basic science studies (1) demonstrated that opiates could produce peripheral analgesia, the degree of effect was limited. More recently, a series of clinical studies has demonstrated that peripheral analgesic activity is present in human patients (e.g.2) but the degree of pain relief was, although statistically significant, not clinically profound. The apparent weak nature of peripheral opiate analgesia, however, may simply be a result of the pharmacokinetics of the drugs that have been tested. All of them are capable of crossing the blood brain barrier. That limits the dose of drug that can be given without producing effects within the CNS. We hypothesized that if an opiate is limited in its ability to cross the blood-brain-barrier we would be able to detect profound levels of peripheral opiate analgesia. In the first part of this talk we will discuss data from a study in which a peripherally limited mu opiate agonist (ADL-2-1294) was tested against a newly developed model of hyperalgesia resulting from thermal injury.

Under general anesthesia, the plantar surface of the left hind foot of CAMM Sprague-Dawley rats was exposed to a radiant heat source that produced a mild second degree burn. Two hours after thermal injury the withdrawal threshold of the injured feet was at least 1.5 seconds faster than the threshold on the uninjured, contralateral paw. A modified Hargreaves testing device was used with stimulus intensity set to produce a withdrawal latency, in adapted non-injured skin, within 8 to 10 seconds. Twenty four hours after the thermal injury the absolute value of the mean

difference score (latency in the injured foot minus latency in the normal foot) was greater than 2.5 seconds. Under light halothane anesthesia, ADL-2-1294 was injected (50, 100, 120 ug in 20% cremophor) into the site of thermal injury and anesthesia was immediately discontinued. Withdrawal latencies were measured every 15 minutes for the next two hours. In an additional series of experiments ADL-2-1294 was administered into the non-injured foot and latencies were again determined.

As shown in figure 1, ADL-2-1294 demonstrated a steep dose dependent effect. The effect of the 50 ug dose was no different than vehicle but a significant prolongation of latency to response was caused by the higher doses. At the time of peak effect (30 minutes) the mean difference score had gone from a -2.5 to a + 3.8, i.e., the injured feet, instead of withdrawing 2.5 seconds faster than the normal feet were now withdrawing 3.8 seconds slower that the normal, non-injured feet. ADL-2-1294 had not only blocked the hyperalgesia produced by the thermal injury it had produced a level of analgesia beyond the anti-hyperalgesic effect. Of importance to the second part of this presentation, the analgesic effect was only seen when ADL-2-1294 was injected into the injured foot. No such change in difference scores were observed with drug injection into the normal feet.

An additional indicator of the intensity of the analgesia were the latency measures themselves. In spite of the fact that human observers , within 15 seconds, find the stimulus to be quite painful, 4 of the ten animals that received the 120 ug dose did not withdraw until after 16 seconds and two of them failed to withdraw within the 20 second cut-off time. It was obvious that a significant level of analgesia was present in those animals.

The above results indicate that a significant level of peripheral opiate analgesia can be produced by a peripherally limited mu opiate. We hypothesize that the profound level of analgesia was evident because we were able to produce high enough levels in the periphery without having the drug cross the blood-brain-barrier and cause effects within the central nervous system. We believe that these results demonstrate the great clinical potential for peripheral opiate analgesia. However, as we will discuss in the remainder of the talk, even greater levels of analgesia may be observed in rats with other genetic backgrounds.

A PITFALL: As we completed the above studies we were informed that the supplier of the animals (CAMM) was going out of business so we were forced to change to another source of the same strain of rats (Sprague-Dawley). Our next project involved a determination of when, after thermal injury, the ADL-2-1294 induced analgesia was first observed. As we conducted those studies it became apparent that the drug effects were very different in these new animals. ADL-2-1294 appeared to be more potent in the new animals and, of even greater interest, it appeared to work as well in the absence of tissue damage as it did in the presence of damage. As shown in figure 2, the drug effect on mean difference scores was greater in the normal skin of these Harlan rats than it was in the injured skin of the CAMM rats, as shown in figure 1. Recall that in the CAMM animals ADL-2-1294 was only efficacious in the presence of thermal injury. We are now investigating differences among several suppliers of rats (Harlan, Charles River, Taconic) and have data suggesting that there may be differences in the degree of efficacy of ADL-2-1294 among animals from different suppliers . Unfortunately, there are no CAMM animals available to examine the underlying causes of the difference.

We are not aware of similar reports for peripheral drug actions but certainly such animal differences have been reported for centrally acting analgesics. We will discuss the implications of such differences to our efforts to examine the importance of peripheral opiate analgesia.

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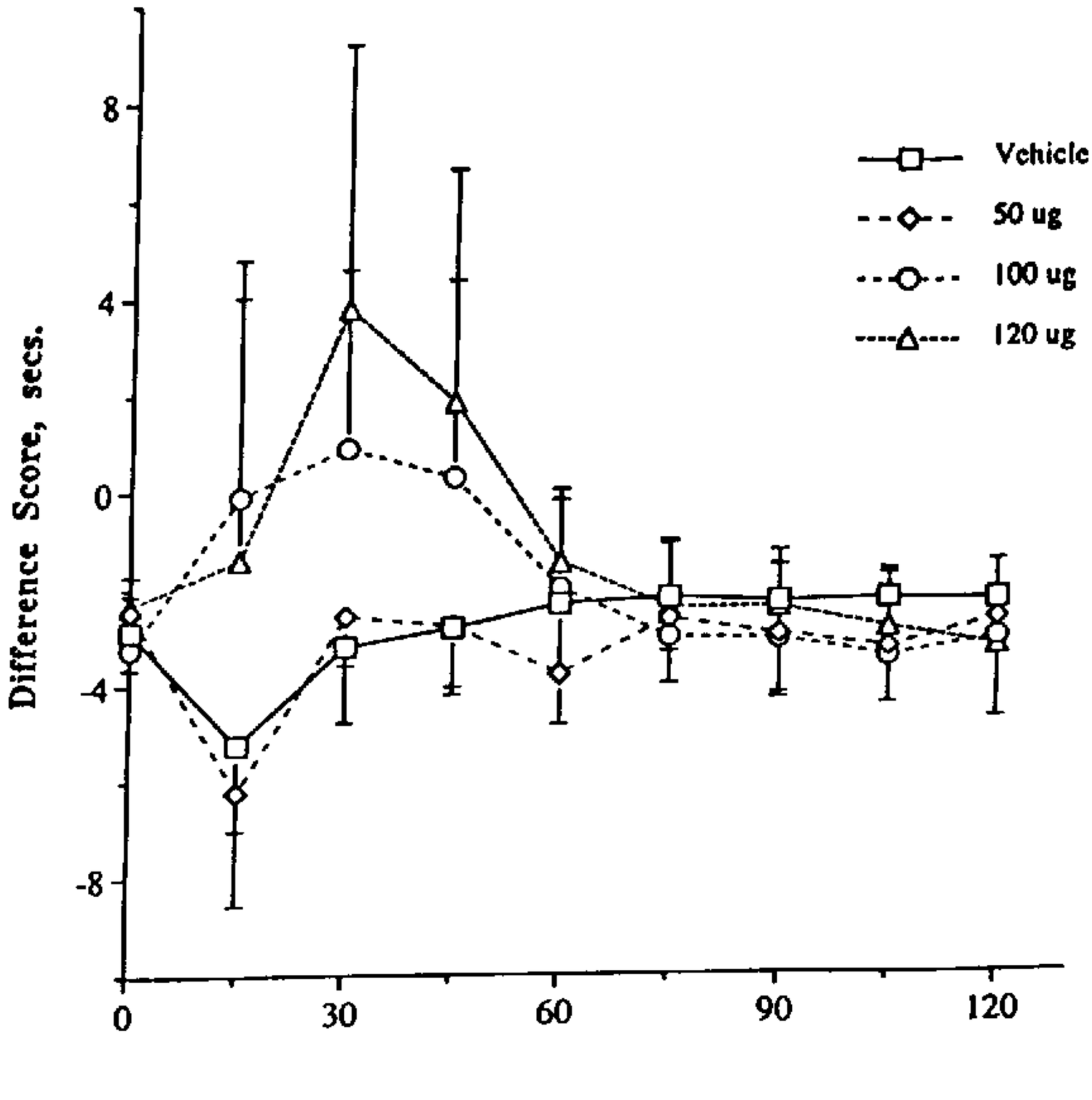
1. Prostaglandins 18: 191-200, 1979

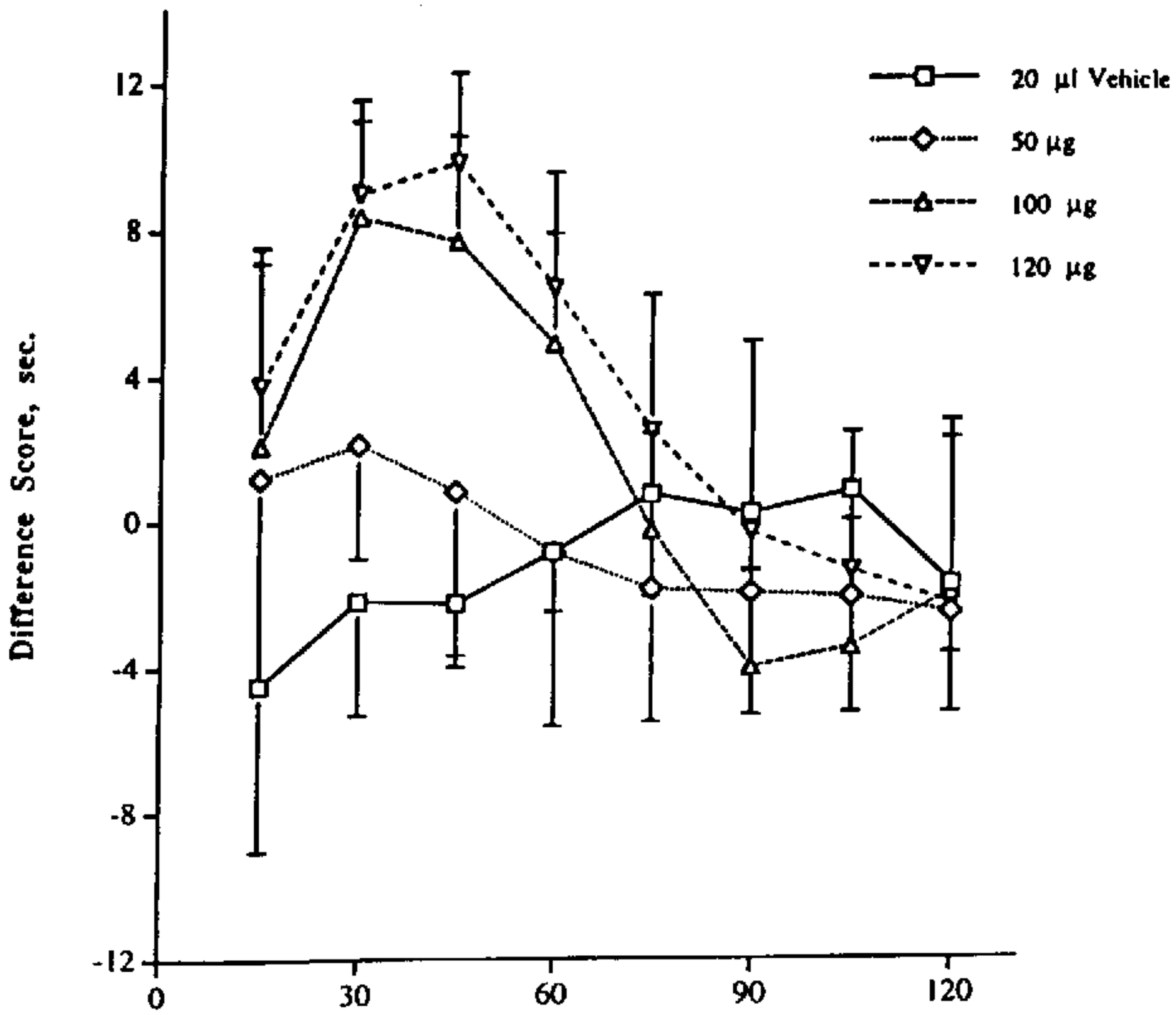
2.Anesth. Analg. 84: 1313-1317, 1997

Figure 1



The mean difference scores (with standard deviations) are plotted for the doses of ADL-2-2194 indicated. Drug was injected, under light general anesthesia, into the injured foot 24 hours after thermal injury was produced. There was still some residual anesthetic effect at the 15 minute time point. However, at the 30 minute time point the analgesic efficacy of the 120 ug dose is quite apparent.

Figure 2



In contrast to the data in figure 1, the data in this figure come from non-CAMM animals that have been injected in non-injured skin. Remember that in CAMM animals ADL-2-1294 had no effect in normal skin. We see, however, that in Harlan animals ADL-2-1294 is actually more potent in normal skin than it was in injured skin of CAMM animals. Since these animals were not injured there was no difference score at time 0. However at the peak of effect, 45 minutes for the 120 ug dose, the absolute value of the mean difference score was approximately 10. In the injured CAMM animals the absolute value was only approximately 6.5. For reasons we do not currently understand, CAMM animals were less sensitive to peripheral opiate actions.

OPIOID PEPTIDE ANALOGUES AS A POTENTIALLY NEW GENERATION OF ANALGESICS

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The discovery of endogenous opioid peptides over twenty five years ago, provided a new impetus for understanding the modulation of pain transmission. Since their discovery the endogenous opioid peptides along with other peptide superfamilies have served as very important tools for pharmacological and biological studies. The early application of opioid peptide analogues as analgesics produced disappointing results and discouraged subsequent interest in harnessing peptides as analgesics. Nevertheless, recent pharmacological results of newly synthesized peptide analogues prompt reconsideration of this group of compounds as potential new generation of analgesics.

The potential applications of peptides as analgesics targeted to "sites of action" techniques; as agents targeted for preferential actions in the periphery outside the CNS; and as compounds that modulate receptor selectivity of nonpeptide moieties will be discussed.