DYNORPHIN-(1-13) SUPPRESSES HEROIN WITHDRAWAL SYMPTOMS IN 6 ADDICTS

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ABSTRACT
Six cases heroin abusers, during withdrawal, were given iv normal saline and dynorphin-(1-13), respectively. After saline a slight placebo effect was noticed. When dynorphin-(1-13) given iv, withdrawal scores were lowered significantly. This result suggests that dynorphin-(1-13) can suppress withdrawal syndrome. The side effects due to dynorphin-(1-13) were very minimal.

KEY WORDS dynorphin; heroin; withdrawal symptoms; patients.

Recently the porcine pituitary peptide, dynorphin, was purified and found to have potent opiate-like agonist properties in the guinea pig ileum and mouse vas deferens bioassay\(^1\). The sequence of the first 13 amino acids in this peptide has been determined and an abbreviated peptide dynorphin-(1-13) containing leu-enkephalin at its N-terminal end, followed by the C-terminal extension-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-OH has been synthesized.\(^2\) This synthetic product was confirmed to be potent by the guinea pig ileum assay but was rather weak in the mouse tail-flick test\(^3\). The reason for its weak activity in vivo may attribute to rapid degradation by amino-peptidase and carboxypeptidase\(^4\). Although dynorphin-(1-13) is of low activity in vivo, it can inhibit both morphine and \(\beta\)-endorphin induced analgesia. However, unlike narloexone, it does not precipitate jumping in dependent animals but can effectively suppress spontaneous withdrawal jumping\(^5\). In view of the above finding, we thought it would be appropriate to investigate whether dynorphin-(1-13) could attenuate the withdrawal syndrome of heroin abusers. This paper reports our preliminary findings on the use of dynorphin-(1-13) to relieve the withdrawal syndrome of 6 heroin addicts.

MATERIALS & METHODS
The patients were 6 male volunteer heroin abusers with long standing history. Informed consent was obtained. Their age ranged from 22 to 55 years, with the...
$\bar{x} \pm SD = 32.3 \pm 11.4$ years. The duration of addiction varied from 5 to 14 years, that was 9.7 $\pm$ 3.0 years. The amount of money spent per day per person was from HK$80 to HK$300, which was HK$143.3 $\pm$ 90.7. A packet of no. 3 heroin costs between HK$50 to HK$100 (net 0.15 to 0.3 g). All of the subjects started taking heroin by inhalation and then slowly changed to iv injection afterwards. Two patients injected themselves t.i.d., the rest q.i.d. All of them had received previous treatment in the rehabilitation centres in Hong Kong but relapsed. Three of them were on methadone maintenance in addition to their heroin intake.

After admission to the hospital, complete physical examination was carried out. Urine was examined to establish that the patients were on drug(s). Prior to admission to the hospital, all the patients invariably had taken heroin and as a result showed no sign of abstinence. After admission, no medication was given, except only when patient could not sleep, then one tablet (2 mg) of flunitrazepam (Rohypnol) was given. The patients were usually admitted to the hospital at noon on the day prior to the investigation. Upon admission, they were taught to mark a scale indicating the severity of the withdrawal syndrome according to a modified scoring procedure(6). Scoring was also done parallely by the nurses (observers) on duty when the investigation was carried out.

The following morning the patients were observed for symptoms and signs of withdrawal. When it was established that they had a high withdrawal syndrome (score of 75 or more), 2 ml of normal saline (NS) were injected iv over an interval of 2 min and withdrawal symptoms were scored in every 15 min for 1 h. At the end of this period, dynorphin-(1-13) (Peninsula Labs, Belmont, CA) was given iv at 125 μg/kg in 2 ml NS. Scoring of withdrawal was carried out every 15 min for a period up to 1 h after the iv. Side effects due to the iv of dynorphin-(1-13) were also monitored continuously by doctors on duty. The patients, the nurses and the doctor who gave the iv had no knowledge on the nature of the solutions. Withdrawal scores were analyzed using the Student's t-test.

**RESULT**

After admission to the hospital (see Table 1) it was found that the scores for the withdrawal syndrome of the patients were mild. There was no difference in the patients' and nurses' (observers) rating. When the patients had a full blown withdrawal syndrome, usually in the following day, the scores were double those of admissions (i.e, before NS). After the administration of normal saline (NS) withdrawal scores were generally lowered, suggesting that there may be a mild placebo effect. However, by the t-test, the reduction of scores was not significant.

After the iv of dynorphin-(1-13), the average score recorded by the patients was lowered by 30% compared with that obtained before NS. Scoring carried out by the nurses produced similar results. In view of these findings dynorphin-(1-13) is likely to be active in suppressing withdrawal in human. It is also our experience that dynorphin-(1-13) not only suppresses withdrawal syndrome but its duration of
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action is much longer than that of β-endorphin (unpublished data), DALA(7) and DAMME(8). Right after iv dynorphin-(1-13), the patients usually feel more relaxed. In order to determine the potency of dynorphin-(1-13), patients were asked to state the amount of money they spent on heroin which would given the equivalent potency of the iv dynorphin. They would say that it was about half the amount of the money they spent per day. After 20-25 min, the response was increased to the equivalent of the whole amount of heroin intake per day. These results suggest that the patients were satisfied with dynorphin-(1-13) even though there was no feeling of euphoria.

45 min after iv dynorphin-(1-13), minor symptoms and signs of withdrawal began to reappear, if not counteracted, a full blown picture occurred after 3 ½ — 4 h. The side effects (Table 2) observable after iv dynorphin-(1-13) were only noted when the patients were questioned. Otherwise, they showed no complaint at all. The feeling of warmth and flushings of the body, especially over the face were seen in 5/6 patients. This lasted 10 min and then other side effects were noted. These side effects were similar to those of β-endorphin, DALA and DAMME but much milder. No catatonia was noticed and none of the patients complained about severe formication of the extremities and the lower part of the back. Only 2 patients complained of precordial formication.

DISCUSSION

It has been observed previously that dynorphin-(1-13) could inhibit morphine or β-endorphin induced analgesia despite of not having appreciable analgesic activity itself. It showed no inhibitory effect on D-alal5-D-leu6-enkephalin or D-Ala2,-MePhe4, Met-(0)5-ol-enkephalin induced analgesia in naive animal. However, it did effectively block the spontaneous withdrawal jumping in morphine dependent animals(5). Our finding on the suppression of the withdrawal syndrome after iv dynorphin-(1-13) on heroin abusers supported the finding(5) of suppression of the withdrawal jumping on morphine dependent animals.

The question is, how dynorphin-(1-13), when itself is not an analgesic, is able to attenuate the withdrawal syndrome of heroin abusers. Dynorphin-(1-13) when given to animals up to 100 times that of morphine sulphate on a molar basis resulted in no development of dependence (9). In heroin addiction both the level of β-endorphin and dynorphin are probably suppressed. After dynorphin administration, an enhancement of β-endorphin content around the opiate receptor sites may be induced. As this process continues the level of β-endorphin in the opiate receptors is brought back to its normal state thus attenuating the withdrawal syndrome. When dynorphin-(1-13) is administered, its action on withdrawal is immediate. This implies that it probably can penetrate the blood brain barrier very rapidly since it is known that this peptide has a very short half-life in vivo.

The side effects of dynorphin-(1-13) were very minimal and the only complaint that the patients had, which occurred on 2 occasions, was the precordial formica-
tion. Why was it limited only to the precordial region requires further investigation.
In contrast, when β-endorphin, DALA and DAMME were administered the formication were all over the body, mainly in the extremities, especially in the lower part of the body. Catatonia was present after β-endorphin(10) and DALA(7) injection, but not in DAMME(8) or dynorphin-(1-13).

Based on our observations, it would be reasonable if a long acting dynorphin-(1-13) could be synthesized and used for detoxification of opiate addiction or even for the treatment of chronic pain, when applied in conjunction with minute amount of opiates. Even with its present structure, dynorphin-(1-13) could enhance the action of morphine as already reported(5).

It is our conclusion that dynorphin-(1-13) does alleviate the withdrawal syndrome of heroin abusers and the side effects are inconsequential.

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Table 1. Effect of dynorphin-(1-13) on opiate withdrawal scores in 6 addicts (x ± S.D.)

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Before NS</th>
<th>After NS</th>
<th>After Dyn-(1-13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>46 ± 17</td>
<td>81 ± 9</td>
<td>72 ± 9</td>
<td>56 ± 10*</td>
</tr>
<tr>
<td>Nurse</td>
<td>47 ± 14</td>
<td>74 ± 6</td>
<td>65 ± 8</td>
<td>52 ± 6**</td>
</tr>
</tbody>
</table>

* 0.01 < P < 0.001 ** P > 0.001 compared with before NS

Table 2. Side effects after iv dynorphin-(1-13)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling warmth</td>
<td>5</td>
</tr>
<tr>
<td>Flushing</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>2</td>
</tr>
<tr>
<td>Sweating</td>
<td>2</td>
</tr>
<tr>
<td>Thirsty</td>
<td>2</td>
</tr>
<tr>
<td>Tiredness</td>
<td>2</td>
</tr>
<tr>
<td>Precordial formication</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
</tbody>
</table>