# Epinephrine Potentiates the Analgesic and Antidepressant Effects of Polyvinylpyrrolidone and Cholecystokinin due to Stimulation of Afferents in the Gastric Mucosa

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Treatment with epinephrine, polyvinylpyrrolidone, and cholecystokinin in the minimum effective doses produced maximum analgesic and antidepressant effects and caused bradycardia in rats. Administration of epinephrine in combination with polyvinylpyrrolidone or cholecystokinin in threshold doses ($^1/_{10}$-$^1/_{25}$ of the minimum effective dose) produced maximum analgesic and antidepressant effects, but did not cause bradycardia. The potentiating effect of epinephrine is related to stimulation of afferents in the gastric mucosa.

**Key Words:** *epinephrine; cholecystokinin; polyvinylpyrrolidone; stomach; afferents*

Stimulation of pressor cardiopulmonary vagal afferents induced by systemic administration of colloid plasma substitutes polyvinylpyrrolidone (PVP) and dextran in high doses, as well as stimulation of subdiaphragmatic vagal afferents with high doses of gastrointestinal hormone cholecystokinin (CCK) produced maximum analgesic and antidepressant effects [3,10-12].

Intramuscular injection of epinephrine in high doses also produces maximum analgesic and antidepressant effects due to stimulation of subdiaphragmatic vagal afferents caused by epinephrine-induced activation of afferents in the gastric mucosa [1,3]. However, the agents stimulating vagal afferents cause a variety of side effects and complications (bradycardia, bronchospasm, dyspepsia, spastic abdominal pain, *etc*.) related to reflex hyperactivation of vagal afferents [2,4,6,7,9].

Low-intensity stimulation of subdiaphragmatic vagal afferents upon activation of afferents in the gastric mucosa with epinephrine in threshold doses ($^1/_{10}$ of the minimum effective dose, MED, inducing the maximum analgesic and antidepressant effects) does not cause bradycardia, but produces a small analgesic and antidepressant effect (3-5% of the maximum effect) [1-3].

Here we studied the potentiating action of epinephrine on analgesic, antidepressant, and peripheral vagal effects of PVP and CCK in threshold doses.

## MATERIALS AND METHODS

Experiments were performed on male outbred albino rats weighing 180-200 g. Each group consisted of 8-10 rats. The study was conducted at 10.00-16.00. Epinephrine, PVP (molecular weight 12,600±2700), and CCK (Sigma reagents) were injected intramuscularly 30 min before the start of the study. Some animals received PVP or CCK in combination with epinephrine in the threshold dose (0.012 mg/kg, $^1/_{10}$ of MED). Control rats received intramuscular injection of 0.2 ml distilled water.

The analgesic effect of the test compounds was estimated from the increase in the latency of the tail-flick response [1]. The antidepressant effect was studied in a modified 2-day Porsolt test [3]. The duration of immobility was recorded during 10-min forced swimming.

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For quantitative evaluation of antidepressant and analgesic activity, we calculated MED of epinephrine, PVP, CCK, PVP+epinephrine, and CCK+epinephrine that induced the maximum antidepressant (immobility duration <40 sec) and analgesic effect (tail-flick latency >30 sec) [1,3]. For evaluation of the role of gastric mucosa afferents in epinephrine-induced potentiation of the analgesic and antidepressant effects of CCK and PVP, we administered intragastrically local anesthetic lidocaine (1% solution, 0.5 ml) or ganglionic blocker hexamethonium (0.2 mg/kg) 30 min before combined treatment with the test compounds [1,3]. The side effects associated with activation of vagal efferents were evaluated by the degree of bradycardia 30 min after individual or combined administration of the test compounds [2].

The results were analyzed by methods of variational statistics.

## RESULTS

Epinephrine in MED (120-130 μg/kg intramuscularly) induced the maximum analgesic and antidepressant effects in rats. Treatment with epinephrine, PVP, and CCK at MED also produced the maximum analgesic and antidepressant effects (Table 1). Epinephrine and PVP in MED caused severe bradycardia and decreased the heart rate (HR) by 197 and 167 bpm, respectively (Fig. 1). The degree of bradycardia was lower after administration of CCK in MED (decrease in HR by 92 bpm compared to the control).

Hence, administration of CCK, epinephrine, and PVP in high doses producing strong stimulation of subdiaphragmatic and cardiopulmonary vagal afferents [1-3,11] not only induced maximum analgesic and antidepressant effects, but also caused severe bradycardia. It was probably related to reflex activation of cardiac vagal efferents [2,6,9].

Treatment with PVP, epinephrine, and CCK in threshold doses ($^1/_{10}$-$^1/_{25}$ of MED) had a small analgesic and antidepressant effect (2-5% of the maximum effect), but did not cause bradycardia.

Administration of epinephrine (threshold dose 12 μg/kg, $^1/_{10}$ of MED) in combination with PVP or CCK allowed us to decrease MED of PVP and CCK by 10-11 and 20-25 times, respectively (Table 1). These doses correspond to threshold doses of PVP and CCK that induce only a small analgesic and antidepressant effect during individual administration. Combined treatment with CCK and epinephrine did not decrease HR compared to the control. Combined administration of PVP and epinephrine caused mild bradycardia. The degree of bradycardia was 3-fold lower compared to that observed after individual treatment with epinephrine or PVP in MED (Fig. 1).

**TABLE 1.** MED of PVP (mg/kg) and CCK (μg/kg) Producing Analgesic and Antidepressant Effects (*M*±*m*)

| Compound | Tail-flick test | Porsolt test |
|---|---|---|
| PVP | 220±26 | 212±23 |
| PVP+epinephrine | 23.0±2.6 | 20.0±2.4 |
| PVP+epinephrine+lidocaine | 280±34 | 265±29 |
| PVP+epinephrine+ hexamethonium | 225±30 | 220±27 |
| CCK | 2.00±0.24 | 2.10±0.25 |
| CCK+epinephrine | 0.080±0.009 | 0.010±0.012 |
| CCK+epinephrine+lidocaine | 3.50±0.39 | 3.40±0.38 |
| CCK+epinephrine+ hexamethonium | 2.40±0.31 | 0.250±0.034 |

Preliminary anesthesia of the gastric mucosa with lidocaine, as well as blockade of intramural ganglia with hexamethonium, which prevented epinephrine-induced stimulation of afferents in the gastric mucosa [1,3], completely abolished the maximum analgesic and antidepressant effects of combined treatment with epinephrine and PVP or CCK (Table 1). Hence, epinephrine in the threshold dose stimulates afferents in the gastric mucosa and, therefore, potentiates small analgesic and antidepressant effects of PVP and CCK in threshold doses. Under these conditions PVP and CCK produced the maximum effect, which was observed after individual intramuscular injection of the test compounds in MED. It can be hypothesized that small analgesic and antidepressant effects induced by low-intensity stimulation of cardiopulmonary and subdiaphrag-

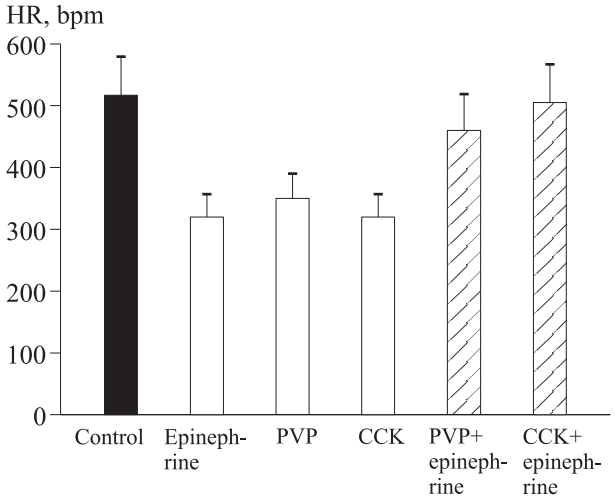


**Fig. 1.** Effects of individual or combined treatment with PVP, CCK, and epinephrine on HR in rats.

matic vagal afferents with PVP and CCK in threshold doses, respectively, are potentiated by additional low-intensity stimulation of subdiaphragmatic vagal afferents due to activation of afferents in the gastric mucosa by epinephrine in threshold doses.

The proposed method for combined pharmacological low-intensity stimulation of subdiaphragmatic and cardiopulmonary vagal afferents is safer in therapy of depression and pain compared to widely used clinical techniques of intensive electrical or pharmacological monostimulation of vagal afferents. This procedure does not cause side effects associated with simultaneous activation of vagal efferents typical of potent vagal stimulation [2,5,6,8,9].

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