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Effect of tiapride on electroacupuncture analgesia

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ABSTRACT Tiapride icv 400 μg / rabbit exhibited analgesic and synergistic effects on electroacupuncture analgesia (EAA) in rabbits. Both electroacupuncture (EA) and tiapride (icv 400 μg / rabbit) enhanced the β-endorphin-like immunoreactive substance (β-EPIS) level in cerebrospinal fluid (CSF) measured by radioimmunoassay (RIA). When EA and tiapride were used in combination, a further increase of β-EPIS content was found. The results suggested that promotion of β-EPIS release by tiapride may be one of the mechanisms of synergistic effect of tiapride on EAA.

KEY WORDS tiapride; beta-endorphin; acupuncture; analgesia; radioimmunoassay

Endogenous opioid peptide in the central nervous system (CNS) played important roles in electroacupuncture analgesia (EAA)[1,2]. Tiapride was applied in clinical therapy as an analgesic[3]. It was found that the content of β-endorphin in plasma was increased when tiapride was injected iv in human[4]. Therefore, we observed the effect of tiapride on EAA in rabbits, and simutaneously measured the contents of β-endorphin in cerebrospinal fluid (CSF) of rabbits by radioimmunoassay (RIA) to demonstrate the changes of β-endorphin contents after tiapride and / or electroacupuncture (EA) administration, and to elucidate the mechanism of the effect of tiapride on EAA.

MATERIALS AND METHODS

Tiapride was synthesized by Prof LIU Yi-Sun (Shanghai Medical University). Bacitracin and RIA kit for β-endorphin were purchased from Sigma Chemical Co and the Second Military Medical University respectively.

New Zealand Rabbits (bred by Shanghai Medical University) of either sex, weighing 2.1 ± SD 0.1 kg were used.

Nociceptive test and electroacupuncture Potassium iontophoresis method served for measurement of pain thresholds in rabbits[2], and rabbits with pain thresholds < 1 mA were used. Unilateral "Hegu" point (midpoint of medial edge of 2nd metacarpal of forepaw) and "Waiguan" point (dorsum of forelimb, 12 mm above wrist joint along the medium line between radius and ulna) of each rabbit were electrically needled (3 mm in depth) for 30 min by EA apparatus (Model G-6805-2), at the frequency of 3 Hz with the intensity of inducing slight trembling of forelimb. In control group, sham needle was applied without electrical stimulation. Pain thresholds were observed for 60–100 min, at the intervals of 3–40 min before and after tiapride and / or EA administration.

Icv of tiapride and CSF collection The rabbits were anesthetized with iv sodium pentobarbital 30 $mg \cdot kg^{-1}$. After the head was positioned in a stereotaxic apparatus to right angle, the plastic cannullae (1.0 mm od, 0.6 mm id) were implanted into lateral cerebroventricle (AP_0, L / R_3, $H_{6.5}$) and the 4th ventricle (P_{13}, $L / R_{0.5}$, H_0) respectively, according to Sawyer's atlas, then clogged up. Three days after surgery, pain thresholds were tested, and rabbits with baseline pain thresholds > 1 mA were excluded. Tiapride 10 μl (icv) was delivered from micrometer syringe within 1 min. At both the beginning and the 30th min following icv and / or EA, 50 μl CSF were collected within 1 min. CSF samples were mixed with 5

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μl bacitracin (30 μ · ml^{-1}), quickly frozen in dry ice, and stored at −60℃ until assay. In control group, normal saline was injected. At the end of each experiment, the position of the cannula was verified histologically.

Radioimmunoassay CSF β-endorphin levels were measured by double antibody RIA method as described previously[5]. Pellets were counted in FH-408γ counter.

Statistics Results were expressed as $\bar{x}\pm$ SD, and the statistical significance between groups in terms of changes of pain thresholds were calculated by t test.

RESULTS

Effect of tiapride (iv) on EAA Tiapride iv 2.5, 10, 40 mg · kg^{-1} failed to elicit changes of baseline pain thresholds during 100 min after administration. When they were administrated in combination with EA, tiapride (iv) exhibited no effect on EAA (Tab 1).

Effect of tiapride (icv) on EAA Tiapride icv 400 μg / rabbit brought forth analgesic effects. Tiapride icv, given concurrently with EA, potentiated EAA in terms of maximal increase of pain threshold. Tiapride (100 μg / rabbit, icv) induced neither analgesia nor synergistic effect on EAA (Tab 2).

Effects of tiapride (icv) and / or EA on β-EPIS in CSF β-EPIS contents were increased 0.18± 0.15 ng · ml^{-1} ($n=8$) after tiapride (icv 400 μg / rabbit), as compared with −0.02± 0.09 ng · ml^{-1} ($n=8$) in saline

Tab 1. Pain threshold (mA) after tiapride (iv) and / or EA in rabbits. $\bar{x}\pm$ SD, $n=6$. Statistical significance between changes of pain thresholds was examined by t test. $^{*}P>0.05$ *vs* saline; $^{+}P>0.05$ *vs* EA.

	(mg · kg^{-1})	0 min	5 min	15 min	30 min	60 min	100 min
saline		0.70±0.21	0.73±0.30	0.72±0.35	0.70±0.25	0.67±0.23	0.65±0.25
tiapride	2.5	0.73±0.18*	0.82±0.23*	0.78±0.30*	0.75±0.22*	0.80±0.28*	0.74±0.24*
	10	0.77±0.23*	0.77±0.24*	0.85±0.25*	0.67±0.22*	0.77±0.30*	0.69±0.30*
	40	0.79±0.19*	0.82±0.30*	0.76±0.32*	0.66±0.31*	0.73±0.34*	0.69±0.22*
EA		0.70±0.20	0.98±0.29	1.53±0.32	1.15±0.33	0.98±0.30	0.87±0.19
tiapride + EA	2.5	0.68±0.16*	1.08±0.28^{+}	1.6±0.3^{+}	1.4±0.4^{+}	1.08±0.28^{+}	0.99±0.24^{+}
	10	0.66±0.18*	0.9±0.3^{+}	1.6±0.3^{+}	1.2±0.3^{+}	1.1±0.3^{+}	0.9±0.3^{+}
	40	0.70±0.25*	0.97±0.24^{+}	1.42±0.24^{+}	1.1±0.4^{+}	1.0±0.4^{+}	0.9±0.3^{+}

Tab 2. Pain threshold (mA) after tiapride (icv) and / or EA in rabbits. $\bar{x}\pm$ SD, $n=8$. Statistical significance between changes of pain thresholds was examined by t test. $^{*}P>0.05$, $^{**}P<0.05$ *vs* saline; $^{+}P>0.05$, $^{++}P<0.05$, $^{+++}P<0.01$ *vs* EA.

	(μg / rabbit)	0 min	3 min	10 min	20 min	40 min	60 min
saline		0.70±0.20	0.73±0.24	0.75±0.24	0.79±0.25	0.70±0.22	0.74±0.27
tiapride	100	0.78±0.29*	0.74±0.36*	0.74±0.28*	0.83±0.32*	0.77±0.30*	0.75±0.30*
	400	0.75±0.26*	0.71±0.26*	1.05±0.39**	1.06±0.37**	0.94±0.28**	0.86±0.23*
EA		0.60±0.21	0.9±0.4	1.4±0.5	1.6±0.4	1.2±0.5	0.9±0.5
tiapride + EA	100	0.65±0.24^{+}	0.95±0.20^{+}	1.4±0.6^{+}	1.7±0.6^{+}	1.2±0.5^{+}	1.14±0.28^{+}
	400	0.60±0.16^{+}	1.1±0.3^{+}	2.4±0.4^{+++}	2.4±0.6^{+++}	1.8±0.6^{++}	1.5±0.5^{++}

group ($P<0.01$). EA brought about an increase of β–EPIS contents 0.16± 0.21 ng • ml^{-1} ($n=8$) ($P<0.05$ *vs* saline group). When EA was applied together with tiapride, there was a further increase of β–EPIS contents 0.46 ± 0.30 ng • ml^{-1} ($n=8$) ($P<0.05$ *vs* EA or tiapride group).

DISCUSSION

The present results demonstrated that tiapride (icv 400 μg / rabbit) exhibited both analgesia and synergism with EAA. The reason why tiapride (icv 100 μg / rabbit) failed to elicit such effect may be the low dose administration. When tiapride was injected iv, even in high dose (40 mg • kg^{-1}), no such actions were seen. Tiapride, a substituted benzamide, poorly penetrates the blood–brain barrier[6], which may be attributed to the different results between icv and iv of tiapride.

It was previously found that EA effectively alleviated pain and significantly increased lumbar[7] as well as ventricular[8] CSF β–EPIS levels, and there was linear correlation between percentage increase of β–EPIS and of pain threshold[8]. Our results indicated that both EA and icv tiapride markedly induced the increment of β–EPIS content in CSF, which conformed to the previous reports[1,4,7]. When EA and tiapride (icv) were used together, a further enhancement of β–EPIS content was shown. These evidences supported the suggestion that the promotion of β–endorphin release may be one of the mechanisms of potential effect of tiapride on EAA.

It was found that the up regulation of opioid receptors in rabbit brain was accompanied with EAA[9]. This may partially explain the reason why EA brought about an analogous increase of β–EPIS level with a higher increase of pain threshold than that of tiapride (icv).

In the previous experiments, dopamine receptor antagonists were evaluated to be a category of EAA synergists[9,10], and anti–dopaminergic action in CNS contributed to the potential effects of these drugs on EAA. Tiapride, a selective dopamine receptor antagonist[11], potentiated EAA as expected. We have detected contents of monoamines and their metabolites in CSF, and no significant change was found (data not shown). But we are still unable to exclude the involvement of dopamine system in the synergistic effect of tiapride on EAA, and this needs further investigations.

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泰必利对电针镇痛的影响

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提要 泰必利(icv 400 μg/兔)对兔产生镇痛作用，并且加强电针镇痛. 应用放射免疫分析法测定兔脑脊液中 β-内啡肽的含量，结果电针和泰必利(icv 400 μg/兔)均提高脑脊液中 β-内啡肽样免疫活性物质的含量；当电针与泰必利合用时，其含量进一步提高. 提示泰必利加强电针镇痛可能与其促进脑内 β-内啡肽的释放有关.

关键词 泰必利；β-内啡肽；针刺；镇痛；放射免疫测定