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前　言

回顾过去的一年，我院继续坚持“科教兴院”的战略方针，取得了丰硕战果。新开各种各类科研课题50项，正在进行的科研课题累计达187项，通过省科委组织的成果鉴定12项，获山西省科技进步奖7项，在各级各类杂志发表论文390篇，其中中华系列107篇，获国家专利2项。

2000年是世纪交替的一年，是充满机遇和挑战的一年，面对新世纪的挑战，我们将在新一届班子的领导下，遵循“巩固、提高、创新、创效”的宗旨，进一步搞好医疗、教学、科研工作，在获全国“百佳医院”，全国“创建文明行业工作先进单位”基础上，继承山医大二院优良传统，发扬成绩，再创辉煌。

本论文集收集了我院1999年1－11月份在全国各级各类杂志上发表的论文，敬请交流斧正。

编者

目　　录

第一部分　国外杂志　国际会议论文

第二部分　中华系列杂志论文

Involvement of endogenous opioids and ATP-sensitive potassium channels in the mediation of apomorphine-induced antinociception at the spinal level: A study using EMG planimetry of flexor reflex in rats

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ABSTRACT: The effects of intrathecally(i.t.) administered naloxone or glibenclamide, a blocker of adenosine triphosphate-sensitive potassium(K_{ATP}) channels, on the antinociception probuced by i.t. apomorphine were observed by an integrated elecrtomyogram measurement of hindlimb flexor reflex in lightly pentobarbital- anesthetized rats. The results showed that i.t. apomorphine produced a significant and dose-dependent antinociception and that the antinociception produced by i.t. apomorphine could be blocked dose dependently by i.t. naloxone or glibenclamide. The results suggest that endogenous opioids and ATP-sensitive potassium channels might be sequentially involved in the mediation of apomorphine-induced antinociception at the spinal level. © 1999 Elsevier Science Inc.

KEY WORDS: Antinociception, Glibenclamide, Apomorphine, Naloxone, Spinal cord, Rats.

INTRODUCTION

Much evidence has indicated the existence of spinally descending dopaminergic pathways and propriospinal dopaminergic neurons [4, 11]. Radioligand binding studies have shown the presence of specific dopamine receptor sites localized in the dorsal horn and intermediolateral

gray matter [5, 6]. Moreover, several studies have shown that dopamine, either released from the long-descending terminals or from the local spinal neurons, is involevd in the processing of noxious inputs in the spinal dorsal horn[8, 12]. In a previous study, we demonstrated that dopamine exerts antinociceptive effects through D_2 subtype dopamine receptors at the spinal level [17].

Adenosine triphosphate-sensitive potassium (K_{ATP}) channels are widely identified in the central nervous system[1, 2], and some investigations imply an important role of these channels in mediation of the analgesia induced by supraspinal or systemic application of morphine or μ-opioid receptor agonist in mice [19, 20]. Recently, we have demonstrated that endogenous opioids and K_{ATP} channels are involved in the mediation of antinociception produced by intrathecal (i.t.) administration of noradrenaline [15] or carbachol[14]. Thus, it is interesting to determine if the opioeds and K_{ATP} channels might act somehow as general local mediators for the performance of the antinociceptive action produced by different kinds of analgesic agents. In the present study, we examined dopamine-induced spinal antinociception, namely, to test if the spinal antinociception induced by i.t. apomorphine, a mixed dopamine D_1/D_2 receptor agonist, could be affected by a previous injection of naloxone or glibenclamide, a blocker of K_{ATP} channels. The same idea has also been tested and verified by using other behavioral models[13].

MATERIALS AND METHODS

Male Wistar rats (250 – 300g) were used with approval of the Shanxi Committee on Ethics of Animal Research. Animals were anesthetized with sodium pentobarbital (50 mg/kg. i.p.), and i.t. catheters were implanted according to the procedure described previously [23, 25]. Briefly, a polyethylene tubing (PE-10) filled with sterile normal saline (NS) was inserted through a small incision in the atlanto-occipital membrane and advanced 7.5cm caudally to the lumbar enlargement of the spinal card. The tube was sutured to the dorsal neck musculature to secure the placement of the catheter. Upon completion of the experiment, catheter placement was confirmed by pontamine sky blue dye injection(5μl, i.t.).

Apomorphine (Sigma), morphine HCI (Shenyang Pharmaceutical Plant, Shengyang, China), and naloxone (Sigma) were freshly prepared with NS. Glibenclamide (Sigma) was dissolved in 5% Tween 80 in NS. Each drug was injected slowly (1 min) in a volume of 10μl followed by 10μl NS to flush the catheter of the crystal molecular formula. The different dos-

es for each drug had been determined in preliminary experiments to be suitable for the present study.

Experiments were carried out 8 – 10h after initial anesthesia and surgery. Those animals showing any motor deficit after recovering from the surgery were discarded from the study. Rats were reanesthetized with sodium pentobarbital (25 – 35mg/kg, i.p.) followed by maintenance doses of pentobarbital (3 – 6mg/kg/h) given intermittently via an i.p. positioned cannula [22, 25]. Supplemental anesthetic was administered at the first sign of any motor responses such as chewing or limb movements.

The nociceptive hindlimb flexor reflex electromyogram (FR-EMG) was utilized as a analgesiometric test as described by Duysens and Gebels [7]. In brief, two subcutaneous stimulating electrodes were inserted under the skin of the plantar side of the paw with an interelectrode distance of about 3mm. The stimulating electrodes were connected to a constant current stimulator (SEN-3201, Nihon-Kohden, Tokyo) delivering short trains (100 Hz for 50 ms) of monophasic pulses (0.5ms). The current intensity was adjusted to obtain a submaximal FR. Generally, 20 – 25 mA was used. A concentric needle electrode (core diameter 0.1mm, needle diameter 0.41mm) was inserted into the ipsilateral biceps femoris/semitendinosus muscles to record the EMG activity by an electromyograph (MEM-3202, Nihon-Kohden). Paw stimulation was under the control of an IBM-PC computer that also sampled the FR-EMG activity at a sampling rate of 4 KHz. The first 2s of EMG activity was integrated, and the values were used as control for i.t. drug-induced changes (i.e., following i.t. drug administration, 2-s EMG recordings were resumed at 5-or 10-min intervals).

Changes in nociceptive FR-EMG activity after i.t. drug injection were expressed as a percentage of the baseline values (mean ± SEM). Statistical significance was determined by means of analysis of variance. All p values less than 0.05 were considered statistically significant.

For understanding the acting site of drugs, with the relevant dosages used in the present study, we have examined the excitability of hindlimb FR motoneuron pools following local drug injection as described by Floeter and Fields [9]. The testing showed that all the drugs, with even higher dosages than those used in the present study, exerted little effect on the amplitude and latency of monosynaptic reflex of the same flexor muscle, thereby providing evidence that the suppressions of FR following drug administrations in the present study oc-

cur mostly at a premotoneuronal level.

RESULTS

Effects of Intrathecal Apomorphine on the FR-EMG

Intrathecal administration of apomorphine(200, 250, 300 nmol) produced a significant and dose-dependent suppression of FR-EMG. It produced a spinal antinociception, as shown in Fig. 1, whereas i.t. administration of the same volume of NS produced no changes in FR-EMG.

Effects of Intrathecal Glibenclamide on the Antinociception Produced by Intrathecal Apomorphine

Pretreatment with glibenclamide (5, 10, 20 nmol, i.t.) antagonized dose dependently the antinociception produced by apomorphine (250 nmol, i.t.), as shown in Fig. 2A, whereas i.t. administration of glibenclamide (5, 10, 20 nmol) alone produced no changes in FR-EMG (see Fig. 2B).

Effects of Intrathecal Naloxone on the Antinociception Produced by Intrathecal Apomorphine

Pretreatment with naloxone (60, 120, 240 nmol, i.t.) antagonized dose dependently the antinociception produced by apomorphine(250 nmol, i.t.), as shown in Fig. 3A, whereas i.t. administration of naloxone(60, 120, 240 nmol, i.t.) alone produced no effects on FR-EMG as shown in Fig. 3B.

DISCUSSION

Although different kinds of techniques [7, 10, 22, 24] have been used for exploring the antinociceptive or pronociceptive effects of many neuroactive substances at different levels of the brain [8, 16, 19 – 23], the spinal dorsal horn proved to be a key point for the perception and modulation of pain [3, 8, 13 – 15, 24, 25]. Multiple data on the effects of dopamine of apomorphine on spinal nociception were far from univocal [12, 18, 21], although most of them showen an antinociceptive action. The precent study indicates that i.t. administration of apomorphine produced a significant and dose-dependent antinociception of the FR-EMG test, excluding the possibility that the effect of dopamine might result from norepinephrine, which might be derived from the dopamine following its injection. As reported previously, the effect is due to the activation of D_2 receptors [17].

Adenosine triphosphate-sensitive potassium channels have recently been demonstrated to

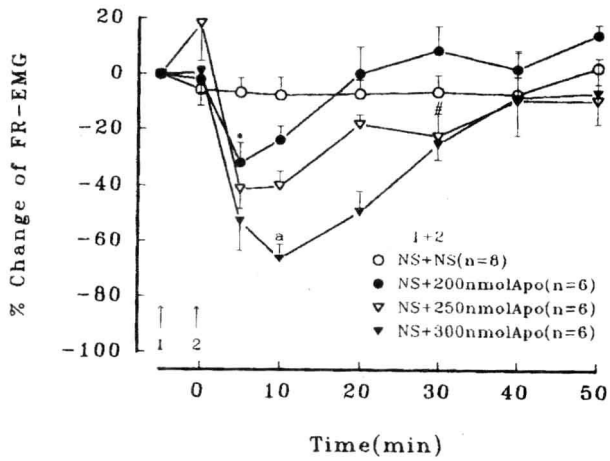

FIG. 1. Percent changes of flexor reflex electromyogram (FR-EMG) (mean ± SEM) after i.t. injections of apomorphine (Apo, 200, 250, 300 nmol). Vehicles were injected as control. Arrows denote the time at which normal saline (NS) or drug was injected. *, $p<0.05$ as compared with the NS + NS group. #, $p<0.05$ as compared with the NS + 200 nmol Apo group. a, $p<0.05$ as compared with the NS + 250 nmol Apo group.

be involved in the mediation of antinociceptive action of morphine given intracerebroventricularly of systemically [19, 20]. In previous studies, we demonstrated that i.t. norepinephrine-induced[15] or carbachol-induced[14] antinociception can be blocked by i.t. naloxone or both endogenous opioids and K_{ATP} channels in the antinociception produced by either norepinephrine of carbachol at the spinal level. In the precent study, it is shown that i.t. naloxone and glibenclamide can also block i.t. apomorphine-induced antinociception, suggesting that the opioids and K_{ATP} channels night also be involved in the mediation of antinociception induced by another kind of spinally used antinociceptive agent (i.e., dopamine agonist). In the hotplate test in mice, Michael-Titus et al. [8] reported that the apomorphine-induced antinociception was antagonized by the dopamine D_2-specific receptor antagonist sulpiride; they also suggested a possible involvement of endogenous opioids acting at μ-receptors in the process. Furthermore, as reported by us previously[15], the antinociception produced by i.t. morphine could be blocked dose dependently by i.t. glibenclamide. Thus, a favorite explanation of our present results might be that apomorphine first activates the local opioidergic neurons, and then the released opioids activate opiate receptors (possibly μ-subtype) to open the K_{ATP} channels , which night be co-assembled with opiate receptors in the

membrane postsynaptic to the local opioidergic terminals. Of course, other explanations cannot be excluded.

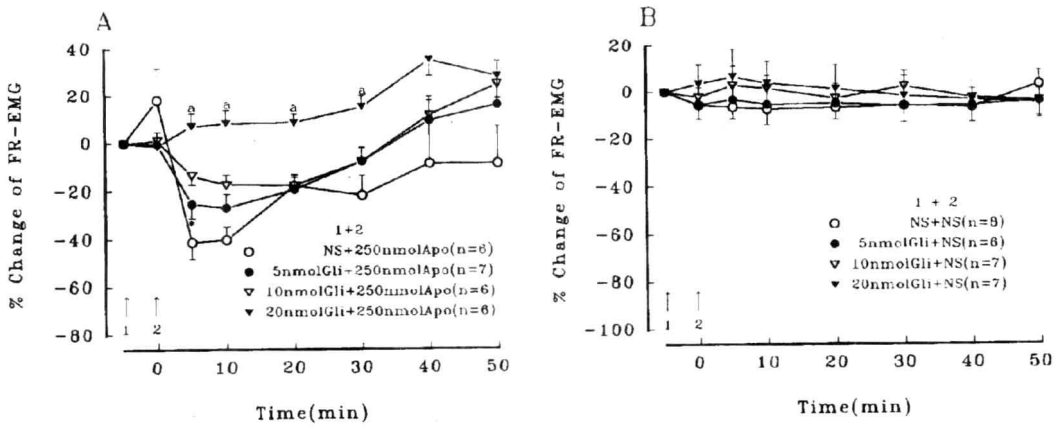

FIG. 2. Percent changes of flexor reflex electromyogram (FR-EMG) (mean ± SEM) after i.t. injections of (A) glibenclamide (Gli, 5, 10, 20 nmol) 5min prior apomorphine (Apo, 250 nmol) and after injections of (B) glibenclamide (Gli, 5, 10, 20 nmol) alone. Vehicles were injected as control. Arrows denote the time at which normal saline (NS) or drug was injected. *, $p<0.05$ as compared with the NS + 250 nmol Apo group. a, $p<0.01$ as compared with the 10 nmol Gli + 250 nmol Apo group.

As the involvement of endogenous K_{ATP} channels has been demonstrated not only in the apomorphine-induced antinociception, as shown by the present study, but also in the cases of norepinephrine-induced [15] and carbachol-induced [14] antinociception, it is hypothesized that the cascade activation of opioids and K_{ATP} channels might be a general mode when many different kinds of antinoception are carried out in the spinal cord.

Furthermore, in previous studies using i.t. adnimistration of drugs, it has been proved that norepinephrine- or morphine-induced antinociception can be prevented by glibenclamide or aminophylline, an adenosine receptor antagonist [24, 25], whereas the antinociception induced by 5′-N-ethylcarboxamidoadenosine, an agonist of adenosine, cannot be blocked by glibenclamide [15]. Therefore, it has been suggested that the release of endogenous adenosine is involved in norepinephrine- or morphine-induced antinociception as another successive link acting behind the activation of K_{ATP} channels. Accordingly, we propose that adenosine might also be involved in apomorphine- or carbachol-induced antinociception. This proposal, of course, remains to be examined further.

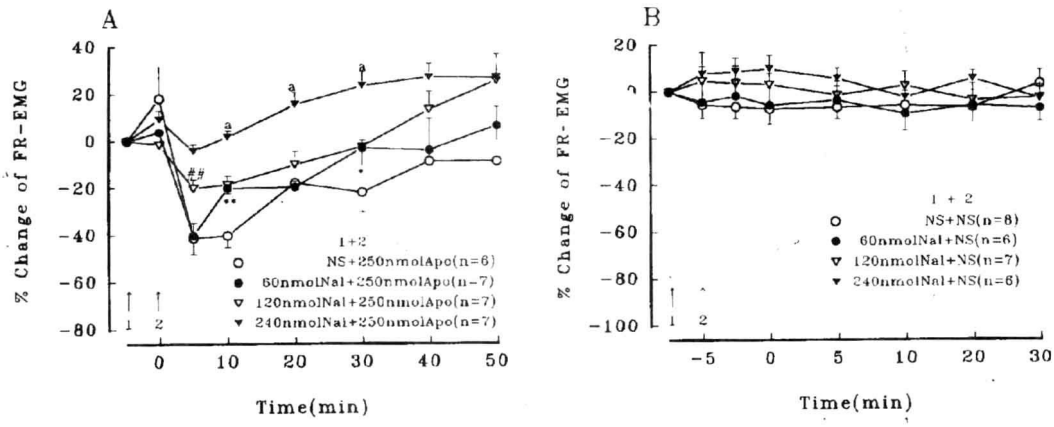

FIG. 3. Percent changes of flexor reflex electromyogram (FR-EMG) (mean ± SEM) after i.t. injections of (A) naloxone (Nal, 60, 120, 240 nmol) 5 min prior to apomorphine (Apo, 250 nmol) and after injections of (B) naloxone (Nal, 60, 120, 240 nmol) alone. Vehicles were injected as control. Arrows denote the time at which normal saline (NS) or drug was injected. *, $p<0.05$. **, $p<0.01$ as compared with the NS + 250 nmol Apo group. ##, $p<0.01$ as compared with the 60 nmol Nal + 250 nmol Apo group. a, $p<0.01$ as compared with the 120 nmol Nal + 250 nmol Apo group.

ACKNOWLEDGEMENTS

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药物性急性间质性肾炎的临床病理及预后因素分析

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（肾内科）

Abstract Objective: To evaluate the clinical presentations, pathological features and

prognoses of drug-associated acute interstitial nephritis. Methods: The data of 20 cases of D-AIN were collected. We analysed the chinical presentations, pathological features and prognoses of 20 patients. Results: Different patients presented different clinical features. No typical clinical features were found. Conclusion: 1. The clinical presentations of D-AIN were diversified and not typical. 2. Renal biopsy was needed to establish the diagnosis. 3. The recovery rate of patients was 85%, and the patients with impaired glomerule by renal biopsy had worse prognosis.

Key words Acute interstitial nephritis Renal biopsy Prognosis

随着抗生素和各种药物在临床上的广泛应用,药物性急性间质性肾炎的发病率日趋增多。由于其早期表现轻,肾功能受损经常被忽略,所以仍不时有漏诊及误诊的现象。我们收集、整理、分析了 20 例 D-AIN 患者的临床病理资料,以期能够为 D-AIN 的诊断及预后判断提供线索。

1 资料与方法

1.1 病例选择 选择 1993 年 4 月～1999 年 4 月间,我院确诊为 D-AIN 患者 20 例。男 13 例,女 7 例。年龄 16～62 岁,平均(42.36)。均有发病前用药史及肾活检的诊断依据,并追踪观察 3 月判断预后情况。

2 观察指标

2.1 药物种类 列举致病药物及相关疾病。

2.2 临术表现 包括发热、水肿、皮疹、少尿、消化道症状、肉眼血尿及关节疼痛,这些症状的患者例数。

2.3 实验室指标 血红蛋白、尿蛋白、镜下血尿、血肌酐、血尿素氮值。

2.4 肾活检所示病变性质及程度。

2.5 预后情况 (1)完全缓解:临床症状及消失,各项化验指标正常。(2)有效:临床症状改善,化验指标好转。(3)无效:临床症状及化验指标均无变化。

3 结果

3.2 药物使用分析 见表 1。

表 1 不同药物致病情况的比较

疾病名称	青霉素例(%)	氨苄例(%)	先锋类例(%)	庆大例(%)	丁卡数(%)	去痛片例(%)	中药例(%)	合计例(%)
少尿型 ARF	2(10)	3(15)		1(5)				6(30)
非少尿型 ARF				2(10)	1(5)			3(15)
NS			3(15)		1(5)	1(5)		5(25)
其它	2(10)	3(15)					1(5)	6(30)
合计	4(20)	6(30)	3(15)	3(15)	2(10)	1(5)	1(5)	20

由上表可知β-内酰胺类似与少尿型 ARF 相关，而氨基甙类既可致少尿型 ARF，又可致非少尿型 ARF，但以非少尿型常见，同时在表现为肾病综合征的患者中使用先锋类药物所占比例较高。

3.2 临床表现分析 见表 2

表 2 药物性急性间质性肾炎临床表现分析

表现症状	例数	百分比(%)
发热	13	65.0
水肿	12	60.0
少尿	9	45.0
皮疹	7	35.0
消化道症状	6	30.0
肉眼血尿	5	25
关节疼痛	2	10

其中仅 1 例同时出现发热、皮疹、关节疼痛三联征。

3.3 实验室检查结果分析 见表 3

表 3 各实验室检查结果分析

检查项目	例数	百分比(%)
BP≥16/12kPa	5	25
BP<16/12kPa	15	75
Hb≥90g/l	6	30
Hb<90g/l	14	70
尿蛋白≥3+	8	40
尿蛋白<3+	12	60
镜下尿中细胞≥50 个/ul	85	17
镜下尿中细胞<50 个/ul	3	15
BUN<7.1mnol/L	14	70
BUN>7.1mnol/L	6	30
Scr≥176.8μmol/L	14	70
Scr<176.8μmol/L	6	30

上表说明 AIN 大部分患者伴有肾功能的异常，及镜下血尿，贫血，但血压增高不明显，而且以中等蛋白尿为多见。

3.4 肾活检所示病理学特征 所有 D-AIN 患者的肾脏病理学表现均有不同程度的间质炎症细胞的浸润，主要为淋巴细胞，以 T 淋巴细胞为主，B 淋巴细胞少见；还可见肾小管上皮细胞变性，坏死及部分肾小管扩张。20 例患者中 10 例表现有小管炎及间质水肿，1 例出现小管萎缩及纤维化。此外还有 8 例患者表现有肾小球的改变，以系膜增殖为主，有此可见新月体形成。