·实验研究·

东北延胡索的药理实验研究

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内容提要 本文研究了东北延胡索的镇痛作用和某些心血管作用，并与延胡索进行了对比。小鼠腹腔或皮下注射30mg/kg、45mg/kg东北延胡索总生物碱，用热板法和扭体法测定，均可显著延长疼痛反应时间及抑制扭体反应发生率。同剂量东北延胡索对扭体反应的抑制作用强于延胡索。东北延胡索延长小鼠缺氧状态下的存活时间，其作用亦强于延胡索。同剂量的东北延胡索与延胡索均能增加离体兔心冠脉流量、抑制心肌收缩力，并且对抗垂体后叶素引起的心电图ST段和T波的变化。

东北延胡索(*Corydalis ambigua Cham.*et Sch.)是元胡的一个野生品种，据报道[1]对胃肠痉挛、瘀血作痛等都有较好的疗效，但是未被载入药典正式使用。为了充分开发野生资源，为东北延胡索的引种栽培和医疗应用提供药理依据，对东北延胡索进行了镇痛和心血管等方面的药理研究，并与延胡索进行了比较。

材料和方法

一、材料：东北延胡索系辽宁宽甸野生药材；延胡索为浙江金华地区栽培品。均采用有机溶媒苯提取方法提得生物碱，配制成盐酸盐溶液。

二、方法：1.镇痛作用：(1)小鼠热板法：选用18～22g雌性小鼠，随机分为6组，每组15只，各组分别腹腔注射东北延胡索30mg/kg、45mg/kg，延胡索30mg/kg、45mg/kg，吗啡10mg/kg及同容量生理盐水，测定疼痛反应时间。(2)小鼠扭体法[2]：选体重18～22g雌雄小鼠60只，随机等分为6组，各组皮下注射药物及生理盐水的剂量同小鼠热板法。给药后1小时，各鼠腹腔注射1%的醋酸0.2ml，记录15分钟内小鼠出现扭体反应次数。

2.常压缺氧耐力：用18～20g小鼠60只，等分为5组，每批实验小鼠体重、性别相同。各组分别腹腔注射东北延胡索30mg/kg、45mg/kg，延胡索30mg/kg、45mg/kg及同容量的生理盐水。给药后20分钟，将小鼠放入150ml广口瓶内，密塞，记录其存活时间。

3.心血管作用：(1)离体兔心灌注实验：体重1.8～3.0kg雌雄家兔12只，按Langendorff氏法灌注心脏，分别从插管注入东北延胡索0.3mg、1.0mg，延胡索0.3mg、1.0mg，间隔一定时间测定每30秒内冠脉流量，同时连续描记心收缩曲线。(2)急性心肌缺血实验：用体重350～550g雌雄豚鼠18只，乌拉坦常规麻醉，描记V_3心电图。稳定后，用慢速电动注射器以0.9ml/分速度在1分钟内将脑垂体后叶素0.5u/kg注入一侧颈静脉内，观察、记录V_3心电图，直至心电图恢复正常为止。然后将18只豚鼠分为2组，分别于颈静脉内注入东北延胡索15mg/kg和延胡索15mg/kg，5分钟时，再依上法给予同剂量的脑垂体后叶素，重复上述实验。比较两次给予脑垂体后叶素后V_3心电图ST段和T波的变化。

结 果

一、镇痛作用：1.小鼠热板法：东北延胡索与同剂量的延胡索的镇痛作用基本相同，均有显著的镇痛作用。见表1。

表1 东北延胡索与延胡索镇痛作用比较

药物 mg/kg	疼痛反应时间(M±SD S)				
	给药前	给药后			
		20′	40′	60′	90′
生理盐水	13.8 ±3.1	14.3 ±3.9	15.4 ±7.0	15.1 ±7.0	14.4 ±4.3
吗啡 10	14.2 ±4.6	30.3 ±13.6	41.2 ±17.0	35.9 ±20.1	26.7 ±14.3
东北延胡索 30	14.2 ±5.0	23.6 ±10.8	26.6 ±10.5	28.5 ±8.1	21.6 ±5.0
45	13.4 ±3.5	28.1 ±20.9	33.7 ±19.4	31.6 ±17.0	24.7 ±19.4
延胡索 30	14.3 ±5.8	23.4 ±8.1	27.4 ±8.5	27.1 ±13.2	23.9 ±10.8
45	13.8 ±4.3	23.5 ±15.5	30.0 ±16.3	26.8 ±12.0	22.8 ±11.6

注：除生理盐水组外，给药后P值均＜0.05。动物数n=15

2.小鼠扭体法：东北延胡索两剂量组扭体次数为7.5±6.3、0，与生理盐水组(33.0±7.9)比较，有非常显著的差异($P<0.01$)；分别与延胡索两组(15.5±9.5、12.2±7.0)比较，镇痛作用也明显强于延胡索。

二、常压缺氧耐力实验：如表2所示。东北延胡索两组与生理盐水组比较，具有非常显著差异；分别与延胡索比较，存活时间也明显延长。

表 2　东北延胡索与延胡索延长小鼠存活时间的比较

药　物(mg/kg)		存活时间(M±SD min)	延长(%)
生理盐水		15.9±2.4	
东北延胡索	30	27.5±10.0**	72
	45	38.5±15.6**	142
延胡索	30	17.3±2.8	8.8
	45	20.4±5.5*	28

注：*、**，与生理盐水组相比，分别为 $P<0.05$ $P<0.01$，$n=12$

三、心血管作用：1.离体兔心灌注实验：(1)对心肌收缩力的影响。东北延胡索与延胡索均可明显减弱心肌收缩力，表现为心肌收缩曲线的振幅明显降低，而且二者剂量相同，作用强度亦相近。见表3。

表 3　东北延胡索减低心肌收缩振幅的比较

药　物(mg)		心肌收缩振幅(M±SD cm)		
		给药前	给药后	减少值
东北延胡索	0.3	4.6±1.7	2.5±1.7	2.1±0.7
	1.0	4.0±2.1	0.9±1.4	3.0±1.7
延胡索	0.3	3.7±1.4	2.6±1.7	1.2±0.7
	1.0	3.9±2.4	1.4±1.0	2.5±1.7

注：各组给药后值与给药前值相比，均为 $P<0.01$，$n=12$

表 4　东北延胡索与延胡索增加冠脉流量的比较

药　物(mg)		冠脉流量(M±SD ml/30s)		
		给药前	给药后	增加值
东北延胡索	0.3	6.9±3.1	16.0±5.9	9.2±4.5
	1.0	7.1±3.5	19.9±7.6	12.8±5.2
延胡索	0.3	7.2±3.8	12.7±3.8	5.6±3.1
	1.0	6.4±2.4	18.0±5.5	11.6±4.8

注：各组给药后值与给药前值相比，均为 $P<0.01$，$n=12$

表 5　东北延胡索与延胡索对抗 ST-T 的比较

药物(mg/kg)	对抗作用	上移、增高最大值(M±SD mm)		减少值(M±SDmm)
		给药前	给药后	
东北延胡索 15	ST段	2.83±1.29	1.61±1.08	1.22±1.59
延胡索 15	上移	3.22±2.13	1.28±0.93	1.94±1.62
东北延胡索 15	T波	13.11±5.4	7.11±2.52	5.67±5.01
延胡索 15	增高	11.67±7.08	6.61±2.76	5.00±5.37

注：各组给药后值与给药前值相比，均为 $P<0.05$，$n=9$

(2)对冠脉流量的影响，在与心肌收缩力减弱的同时，冠脉流量显著增加，二者作用强度也相近。见表4。

2.急性心肌缺血实验：同剂量的东北延胡索与延胡索作用相近，均可明显对抗由脑垂体后叶素引起的V_3心电图ST段上移和T波增高，如表5所示。

四、急性毒性试验：用18～22g雌雄两性小鼠，每组10只，腹腔给药，按寇氏法统计处理。东北延胡索LD_{50}为252.0mg/kg，95%平均可信限为278.1～225.9mg/kg。同法测得的延胡索LD_{50}为269.2mg/kg 95%平均可信限为304.9～238.2mg/kg。

讨　论

本实验对同样方法提得的东北延胡索、延胡索生物碱进行了镇痛作用的研究，结果表明，均有明显地对抗温度和化学刺激所致的疼痛反应的作用。而且，在小鼠扭体反应实验中，东北延胡索的对抗作用优于延胡索，提示东北延胡索对内脏疼痛的抑制作用强于延胡索是其特点。此外，东北延胡索在提高小鼠常压下对缺氧的耐受能力方面，其作用也强于延胡索。

东北延胡索和延胡索都有明显地扩张冠状动脉血管作用，显著增加离体兔心冠脉流量，同时抑制心肌收缩力；明显对抗脑垂体后叶素引起的豚鼠心电图ST段上移和T波增高。

东北延胡索是延胡索的同种属植物，资源丰富，也含有多种生物碱。本文结果又表明，它与延胡索作用性质相同，有镇痛和某些心血管作用，为治疗气滞血瘀等疼痛性疾病及缺血性心脏病提供了一定药理基础。这些都为开发利用东北延胡索提出了依据。

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Studies on Pharmacological Experiment of *Corydalis Ambigua*

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Using benzene extracted alkaloids of *Corydalis ambigua*, the effect of analgesia and its action on cardiovascular system were studied. This alkaloid was compared with that of *Corydalis yanhusuo* extracted in the same way. The following results were obtained:

1.The effect of analgesia: (1) Heating plate method: Mice were injected intraperitoneally with this extract 30 mg/kg and 45 mg/kg. 20 min. later, the responding time of algesthesia was markedly prolonged and sustained for 90 min. In comparison with the same dose of C. *yanhusuo*, it has the similar effect. (2) Method of cramping in mice: Mice were injected subcutaneously with the same dose of the extract. The frequency of cramping was 7.5±6.3 and 0 within 15 min. respectively. As compared with same dose of C. *yanhusuo*, the frequency of cramping was 15.5±9.5 and 12.2±7.0. Therefore this extract was more potent than that of C. *yanhusuo*.

2. Experiment on anoxia-tolerance in mice: The experimental group was administered intraperitoneally with the same dose of the extract, and showed markedly extended survival time for 72% and 142% respectively. The group of C. *yanhusuo* with the same dose was 8.8% and 28% only.

3. The effect on cardiovascular system: (1) Perfused experiment of isolated rabbit's heart: Either this extract or C. *yanhusuo* administered same dose (0.3 mg and 1.0 mg) would inhibit the myocardial contraction significantly, and increase the coronary flow markedly. (2) Experiment of acute myocardial ischemia: The elevating ST-T wave of lead V_3 produced by pituitrin-induced ischemia in guinea pigs was opposed by intravenous injection 15 mg/kg of this extract. Similar effect was also observed with the same dose of C. *yanhusuo*.

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Studies on Anti-Platelet Aggregation of *Allitridi* in Hypercholesterolemic Rabbits

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Thirty-two New Zealand rabbits weighing 1.5~2.5 kg were divided into three groups: group Ⅰ (the control group, n=10); group Ⅱ (n=11) and group Ⅲ (n=11). They were all fed a common-stock diet. Except for the control group, group Ⅱ received cholesterol (0.5 g/kg body weight) daily, while group Ⅲ was fed 0.5 g/kg of cholesterol plus the *Allitridi* (diallyl trisulfide, 20 mg/kg). Blood cholesterol, platelet aggregation, platelet cAMP and cGMP index were determined by the usual techniques at fixed time. The observation was finished at the end of the 15th week. The rise in serum cholesterol was significantly reduced by *Allitridi* during the 15 weeks period of study. Platelet aggregation in group Ⅱ was significantly higher than that in group Ⅰ ($P<0.05$), while in group Ⅲ, it was close to the control group but significantly lower than that in group Ⅱ ($P<0.01$). There was a negative correlation between platelet cAMP and platelet aggregation ($r=-0.42$, $P<0.05$). Platelet cAMP in group Ⅲ was little higher than that in the control group ($P>0.05$), but significantly higher than that in group Ⅱ ($P<0.001$). There was no difference of platelet cGMP between group Ⅱ and group Ⅲ. It is suggested that *Allitridi* has a powerful anti-aggregating effect on platelet in hypercholesterolemic rabbits and its inhibition of platelet aggregation is mediated by an increase of platelet cAMP.

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Cardiovascular Effects of Anisodamine During Endotoxin Shock in Anaesthetized Dogs

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Experiments were carried out on mongrel dogs anaesthetized with pentobarbital. Escherichia coli endotoxin (5 mg/kg) was given intravenously to produce circulatory shock. In 6 dogs, anisodamine (5 mg/kg) infused intravenously over a period of 60 min. caused increase in heart rate, left ventricular systolic pressure, positive and negative maximum dp/dt and mean arterial pressure. Renal blood flow and urinary outflow also raised. No such changes were observed in the control group of 6 animals which received saline infusion only. The results obtained indicate that anisodamine given at early stage of endotoxin shock improves myocardial contractility.

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