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关键词 碘锡化合物；凝血酶；钙；血小板；依他酸；维拉帕米；卡西霉素

目的：观察 I-65 对家兔血小板胞浆游离钙离子（$[Ca^{2+}]_i$）浓度的影响. 方法：用 Quin 2-AM 荧光探针在体外测定家兔血小板 $[Ca^{2+}]_i$. 结果：$CaCl_2$ 1 mmol·L^{-1} 时，I-65（10，20 和 30 μmol·L^{-1}）使血小板 $[Ca^{2+}]_i$ 分别由 142±22 nmol·L^{-1} 和 124±18 nmol·L^{-1} 减少到 118±20，78±12，40±10 nmol·L^{-1} 和 108±15，77±14，37±14 nmol·L^{-1}. 用依他酸 2 mmol·L^{-1} 络合胞外 Ca^{2+}，I-65 胞内贮存 Ca^{2+} 释放从 52±11 nmol·L^{-1} 减少至 34±9，19±6 和 11±5 nmol·L^{-1}. 另外，I-65 也使胞外 Ca^{2+} 跨膜内流从 91±13 nmol·L^{-1} 分别降至 84±15，58±15 和 28±19 nmol·L^{-1}. 结论：I-65 不仅明显抑制家兔血小板胞外 Ca^{2+} 跨膜内流而且抑制胞内贮存 Ca^{2+} 释放.

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Inhibitory effects of copper-aspirin complex on platelet aggregation[1]

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KEY WORDS copper; aspirin; platelet aggregation; *thromboxane* A_2; *epoprostenol*; *serotonin*; arachidonic acid; adenosine diphosphate; platelet activating factor

AIM: To study the inhibitory effects of copper-aspirin complex (CuAsp) on platelet aggregation. **METHODS:** With adenosine diphosphate the effects of CuAsp on platelet aggregation *in vitro* or *in vivo* were investigated. Radioimmunoassay and fluorophotometry were used to measure thromboxane B_2 (TXB_2) generation from platelets, the levels of TXB_2 and of 6-keto-$PGF_{1\alpha}$ in plasma and the platelet serotonin release reaction. **RESULTS:** *In vitro*, CuAsp inhibited arachidonic acid (AA)-induced aggregation (IC_{50} = 17 μmol·L^{-1}, 95 % confidence limits: 9 − 33 μmol·L^{-1}), the release of 5-HT (IC_{50} = 19 μmol·L^{-1}, 95 % confidence limits: 10 − 30 μmol·L^{-1}), and TXB_2 generation from platelets ($P < 0.05$). CuAsp 10 mg·kg^{-1} ig selectively inhibited AA-induced aggregation, and increased the 6-keto-$PGF_{1\alpha}$ concentration in plasma while decreased that of TXB_2. **CONCLUSION:** CuAsp, *in vitro* or *in vivo*, shows more potent inhibitory effects on AA-induced aggregation than aspirin (Asp), related to the inhibition of platelet cyclooxygenase and the release of active substances from platelets.

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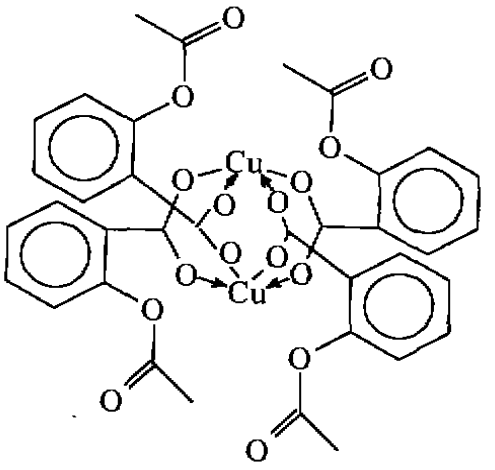
Aspirin (Asp) shows a potent anti-platelet aggregation effect, and is widely applied to the prevention and therapy of thromboembolic diseases, especially ischemic cardiovascular diseases[1]. Asp at higher doses, however, supresses prostacyclin (Pro) synthesis in endothelial cells while inhibits thromboxane A_2 (TXA_2) generation in platelets. To look for a substitute of Asp has become a subject of interest.

Copper aspirinate [Cu_2(aspirinate)$_4$, CuAsp], a copper complex of Asp[2], had not only more potent antipyretic, analgesic, anti-inflammatory, and anti-arthritic effects[2,3] but fewer gastrointestinal side effects than Asp due to the

Cu^{2+}-catalyzed action[2, 4].

In screening trials, we found that CuAsp showed a potent antiplatelet activity, but not manganese aspirinate (MnAsp) or zinc aspirinate (ZnAsp). In this paper, antiplatelet aggregation effects of CuAsp were studied.



Tetrakis-μ-acetylsalicylato-dicopper
[Cu_2(aspirinate)$_4$]

MATERIALS AND METHODS

Rabbits Rabbits of either sex weighing 2.0 – 3.0 kg were obtained from Department of Animal, Kunming Medical College (Certificate number: The Administrative Commission of Medical Experimental Animals of Yunnan Public Health Bureau, № A 11).

Drugs and reagents CuAsp (Cu 14.99 %, C 51.21 %, and H 3.32 %; purity >98 %), MnAsp, and ZnAsp were synthesized by Kunming Institute of Precious Metals. CuAsp was dissolved in 5 % propylene glycol and 1.4 % polyvinyl in water (pH 6.5). MnAsp and ZnAsp were dissolved in water and their pH values were adjusted to 7.4. Crystalline Asp was dissolved in 1 % Na_2CO_3 prior to use, and adjusted its pH to approximately 7.0 with HCl. Both arachidonic acid (AA) and platelet activating factor (PAF) were the products of Sigma Chemical Co. AA dissolved in ethanol, was diluted to 0.5 % solution with 1 % Na_2CO_3 before use. PAF was dissolved in Tris-NaCl buffer containing 0.25 % bovine serum albumin (BSA). ADP (Fluka Chemical Co) was dissolved in phosphate buffer solution (PBS). TXB_2 and 6-keto-$PGF_{1\alpha}$ radioimmunoassay (RIA) kits were purchased from Chinese Academy of Medical Sciences. 5-HT (Fluka Chemical Co) was dissolved in water.

Preparation of platelet-rich plasma (PRP) and platelet-poor plasma (PPP) Rabbit blood from carotid artery was anticoagulated with 3.8 % sodium citrate solution (9:1, vol: vol), spun at 110 × g and 1000 × g respectively for 10 min to obtain PRP and PPP. PPP was used as the reference for platelet aggregation or to adjust the platelet count in PRP, which was kept 5×10^8 cell·L^{-1} in all experiments.

Assay for platelet aggregation

Tests *in vitro* Platelet aggregation studies were performed with ADP[5].

Tests *in vivo* The rabbits were randomly divided into 9 groups (each with 6 rabbits): groups A – D were given ig CuAsp 10, 75, 150, and 300 mg·kg^{-1}, respectively; groups E – H were given ig Asp 10, 75, 150, and 300 mg·kg^{-1}, respectively; and group I was given 0.9 % saline as a control. PRP and PPP were prepared before ig and at 0.5, 1, 2, 3, 4, and 6 h after ig. Platelet aggregation induced by ADP, AA, and PAF were observed *in vivo*.

RIA for TXB_2 and 6-keto-$PGF_{1\alpha}$ in plasma[6,7] At the 2nd and 6th hour after CuAsp 10 mg·kg^{-1} ig, blood 5 mL collected from rabbit carotid artery was anticoagulated with 0.2 mL of heparin-indometacin-saline. Plasma was spun at 1000 × g in ice bath for 10 min. TXB_2 and 6-keto-$PGF_{1\alpha}$ in plasma were extracted from the supernatant and assayed using the RIA kits.

RIA for TXB_2 formation in platelets[6] The extraction and RIA of TXB_2 in the supernatant were similar to those in plasma.

Assay for platelet serotonin release[8] The rabbits were divided into 3 groups of 6 rabbits each. The results were compared with those of 5-HT treated.

RESULTS

Platelet aggregation *In vitro*, MnAsp and ZnAsp had no obvious influence on ADP-, AA-, or PAF-induced aggregation. $CuSO_4$ *in vitro* failed to inhibit ADP-, AA- or PAF-induced aggregation ($P > 0.05$ *vs* control group: 61.8 ± 2.5 % by ADP, 68.0 ± 2.0 % by AA, 55.3 ± 2.1 % by PAF). CuAsp and Asp *in vitro* inhibited AA-induced aggregation in a concentration-dependent manner, with the IC_{50} of 17.2 μmol·L^{-1} (95 % confident limits: 9.1 – 32.8 μmol·L^{-1}) and 27.7 μmol·L^{-1} (95 % confident limits: 15.6 – 49.2 μmol·L^{-1}), respectively; but neither of them did in the presence of ADP or PAF (the aggregation rate in control group: 57.5 ± 2.9 % by ADP, 67.4 ± 3.5 % by AA, and 64.7 ± 3.4 % by PAF) (Tab 1).

$CuSO_4$ 10 mg·kg^{-1} ig slightly inhibited ADP-, AA-, or PAF-induced aggregation (the aggregation rate at 0 h: 54.5 ± 3.7 % by ADP, 65.5 ± 3.4 %

Tab 1. Effects of $CuSO_4$, copper-aspirin complex (CuAsp), and aspirin (Asp) on platelet aggregation induced by ADP, AA, or PAF *in vitro*. $n = 6$ rabbits, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$ *vs* control.

Drug/ μmol·L^{-1}	Platelet aggregant inhibition/% Adenosine diphosphate			Arachidonic acid			Platelet activating factor		
	$CuSO_4$	CuAsp	Asp	$CuSO_4$	CuAsp	Asp	$CuSO_4$	CuAsp	Asp
3.75	2.6±2.1^a	2.2±1.1^a	0.9±0.6^a	2.1±3.7^a	16.4±4.2^a	3.1±2.2^a	2.2±2.9^a	1.1±0.7^a	1.0±1.1^a
7.5	1.1±1.3^a	5.5±2.1^a	3.1±2.2^a	0.7±0.8^a	35.2±1.4^b	12.5±2.8^a	0.9±1.5^a	1.7±0.8^a	1.4±1.7^a
15	2.4±3.1^a	7.2±2.9^a	3.5±1.5^a	0.5±0.7^a	51.3±1.5^b	31.7±2.2^a	2.4±1.8^a	2.5±1.1^a	1.0±1.7^a
30	3.9±2.1^a	8.3±2.6^a	2.6±1.1^a	1.2±1.4^a	60.1±2.3^b	53.7±5.2^b	2.7±2.7^a	4.7±1.9^a	1.5±0.8^a
60	4.6±3.1^a	5.5±2.0^a	2.3±1.4^a	1.2±1.1^a	72.6±2.5^b	68.7±2.4^b	4.6±1.6^a	7.6±2.1^a	2.7±1.6^a
120	5.1±3.7^a	21.9±2.0^a	1.2±0.9^a	0.9±1.2^a	94.3±2.1^b	91.8±3.4^b	6.0±1.8^a	9.8±2.7^a	1.9±1.3^a

by AA, and 52.0±5.9 % by PAF) (Tab 2).

Tab 2. Effects of $CuSO_4$ 10 mg·kg^{-1} ig on platelet aggregation induced by ADP, AA, or PAF *in vivo*. $n = 6$ rabbits, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$ *vs* 0 h.

Time/h	Platelet aggregant inhibition/% Adenosine diphosphate	Arachidonic acid	Platelet activating factor
0.5	2.5±3.6^a	7.2±6.4^a	9.1±4.5^a
1	23.4±12.3^b	21.4±5.7^b	13.9±5.9^a
2	18.3±4.3^b	37.4±10.1^b	19.9±12.2^b
3	19.5±3.6^b	20.4±6.5^b	26.1±7.1^b
4	3.9±3.0^a	7.4±1.9^a	19.4±8.2^a
6	3.9±2.3^a	4.9±2.6^a	6.7±4.1^a

CuAsp 10, 75, 150, and 300 mg·kg^{-1} ig markedly inhibited AA-induced aggregation. Its inhibitory effects were displayed at 0.5 h after ig ($P < 0.05$), maximal at 2 h, and still potent at 6 h ($P < 0.05$). In addition, CuAsp 300 mg·kg^{-1} ig significant inhibited ADP or PAF-induced aggregation by 61.8 ±1.1 % and 71.1±1.7 % ($P < 0.05$), at 2 h respectively, but Asp (300 mg·kg^{-1}, ig) did not (the aggregation rate at 0 h: 57.5 ±4.1 % by ADP, 68.4±3.5 % by AA, and 63.4±3.7 % by PAF) (Tab 3).

Plasma levels of TXB_2 and 6-keto-$PGF_{1\alpha}$

CuAsp (10 mg·kg^{-1}, *ig*) markedly increased the plasma concentrations of 6-keto-$PGF_{1\alpha}$ and signi-

Tab 3. Effects of CuAsp and Asp on platelet aggregation induced by ADP, AA or PAF *in vivo*. $n = 6$ rabbits, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* 0 h.

Drug/ mg·kg^{-1}	Platelet aggregant inhibition/% 0.5 h		1 h		2 h		3 h		4 h		6 h	
	CuAsp	Asp	CuAsp	Asp	CuAsp	Asp	CuAsp	Asp	CuAsp	Asp	CuAsp	Asp
ADP 10	20.0±9.2^a	9.9±4.1^a	22.5±1.9^a	16.3±5.6^a	13.5±2.1^a	12.1±2.2^a	6.4±1.8^a	7.8±4.1^a	3.0±2.7^a	1.8±2.5^a	1.1±1.8^a	3.6±2.1^a
75	11.1±1.4^a	5.8±3.8^a	8.3±2.3^a	13.4±1.5^a	16.5±2.1^a	18.0±1.3^a	13.7±2.1^a	20.7±1.8^a	7.6±1.3^a	15.0±1.7^a	3.3±3.9^a	6.3±2.9^a
150	11.6±1.3^a	6.9±0.6^a	20.5±2.0^a	11.2±1.6^a	30.6±1.1^a	19.4±2.3^a	39.9±2.1^a	17.5±1.7^a	24.9±1.4^a	5.2±1.1^a	5.9±2.9^a	3.1±2.5^a
300	23.5±7.2^a	5.0±3.1^a	38.7±4.8^a	11.7±5.5^a	61.8±1.1^b	22.2±1.4^a	37.2±1.5^a	10.3±3.4^a	6.3±2.4^a	4.5±3.6^a	2.1±1.4^a	1.6±1.9^a
AA 10	94.1±3.9^c	48.3±1.4^a	96.6±2.3^c	51.6±1.8^b	98.1±1.8^c	86.6±2.5^b	97.2±3.3^c	91.4±2.9^b	85.4±1.8^b	77.3±1.5^b	71.0±3.3^b	71.0±3.3^b
75	97.4±1.5^c	91.3±1.9^b	98.1±1.2^c	92.0±2.3^b	98.5±1.1^c	93.3±5.3^b	92.0±2.5^c	90.2±2.4^b	89.5±2.9^b	78.3±1.1^b	87.7±2.0^b	70.7±1.0^b
150	94.9±3.7^c	91.5±1.6^b	96.7±1.0^c	88.8±1.5^b	98.9±1.8^c	96.7±2.3^b	96.1±3.0^c	96.6±1.2^b	93.7±1.4^c	93.4±2.2^b	87.7±1.5^b	85.9±2.6^b
300	92.0±4.5^c	92.7±4.1^b	95.3±3.6^c	93.8±2.4^b	96.8±1.9^c	98.4±2.0^c	96.5±1.6^c	99.5±1.1^c	93.0±2.6^c	96.1±1.3^b	82.6±3.5^b	87.4±2.2^b
PAF 10	5.8±3.9^a	1.7±2.0^a	10.6±5.2^a	2.2±0.9^a	9.9±1.9^a	8.4±1.4^a	8.0±1.7^a	5.9±1.2^a	3.7±0.9^a	2.9±1.4^a	1.2±1.3^a	1.1±1.2^a
75	4.4±2.8^a	5.3±1.3^a	15.9±2.2^a	8.0±3.4^a	13.5±4.1^a	6.2±1.5^a	14.4±1.4^a	3.0±1.7^a	8.8±1.1^a	4.8±3.7^a	4.5±1.8^a	4.6±1.7^a
150	5.0±2.6^a	6.3±1.8^a	9.9±5.4^a	4.8±5.3^a	22.1±5.9^a	2.8±1.5^a	29.3±2.6^a	2.8±1.0^a	15.2±4.0^a	4.9±2.2^a	6.8±4.4^a	2.8±1.9^a
300	65.1±1.2^b	6.7±1.2^a	65.1±1.8^b	8.8±1.1^a	71.1±1.7^b	6.7±1.6^a	39.5±2.5^a	5.5±2.7^a	11.6±5.4^a	15.2±3.3^a	3.6±4.3^a	2.2±2.9^a

ficantly decreased those of TXB_2. In contrast, Asp markedly lowered the plasma concentrations of both TXB_2 and 6-keto-$PGF_{1\alpha}$ (Tab 4).

Tab 4. Effects of CuAsp on plasma levels of TXB_2 and 6-keto-$PGF_{1\alpha}$ *in vivo*. $n = 6$ rabbits, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$ *vs* saline (0.9 %, ig the same volume as groups CuAsp and Asp).

	Saline	CuAsp 10 mg·kg^{-1}	Asp 10 mg·kg^{-1}
TXB_2/μg·L^{-1}			
Before ig	1.53±0.61	1.52±0.62[a]	1.53±0.51[a]
After ig 2 h	1.41±0.71	0.13±0.06[b]	0.51±0.08[b]
After ig 6 h	1.51±0.42	0.22±0.02[b]	0.73±0.06[b]
6-keto-$PGF_{1\alpha}$/μg·L^{-1}			
Before ig	0.52±0.31	0.41±0.31[a]	0.43±0.31[a]
After ig 2 h	0.64±0.31	2.41±1.61[b]	0.22±0.08[b]
After ig 6 h	0.42±0.23	4.13±1.12[b]	0.31±0.09[b]

TXB_2 generation from platelets CuAsp and Asp strongly inhibited AA-induced TXB_2 generation from platelets (Tab 5).

Tab 5. Effects of CuAsp on platelet aggregation and TXB_2 formation induced by AA *in vitro*. $n = 6$ rabbits, $\bar{x} \pm s$. $^bP < 0.05$ *vs* saline.

Drug/mmol·L^{-1}	Platelet aggregation/%	TXB_2/μg·L^{-1}
Saline	68.7±3.5	287.7±86.3
CuAsp 0.12	4.3±1.7[b]	1.1±1.0[b]
Asp 0.12	6.2±2.4[b]	1.2±1.5[b]

5-HT release from platelets CuAsp concentration-dependently inhibited the release of platelet 5-HT, with IC_{50} of 19.1 μmol·L^{-1} (95 % confident limits: 10.4 − 30.5 μmol L^{-1}) (Tab 6).

Tab 6. Effect of CuAsp on 5-HT release from 10^9 platelets induced by AA *in vitro*. $n = 6$ rabbits, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$ *vs* control.

Drug/μmol·L^{-1}	5-HT/ng
0	449±43
3.75	376±17[a]
7.5	342±22[a]
15	264±29[b]
30	170±13[b]
60	128±7[b]
120	0[b]

DISCUSSION

In this study, antiplatelet aggregation effects of CuAsp were investigated by using ADP, AA, and PAF. The results indicate that, on one hand, CuAsp, at a lower dose, markedly inhibited AA-induced aggregation *in vitro* or *in vivo*, which was not obviously influenced by ADP or PAF, demonstrating that CuAsp showed an obviously selective inhibitory effect on the arachidonate pathway of platelet aggregation. On the other hand, CuAsp (300 mg·kg^{-1} ig) significantly suppressed ADP or PAF-induced aggregation, but Asp did not, indicating that anti-platelet action spectrum of CuAsp was wider than that of Asp. Furthermore, in AA-induced aggregation *in vitro*, the IC_{50} value of CuAsp was lower than that of Asp, and inhibitory rates of CuAsp were higher than those of Asp, indicating that CuAsp was more potent than Asp in selectively inhibiting AA-induced platelet aggregation. The inhibitory effects of $CuSO_4$ on platelet aggregation induced by ADP, AA or PAF led us speculate that CuAsp may act via Cu^{2+}-catalyzed action leading to more potent antiplatelet aggregation and wider antiplatelet spectrum than Asp.

The abnormality in TXA_2 and Pro equilibrium will result in platelet aggregation and formation of platelet thrombus[9]. CuAsp strongly decreased AA-induced TXA_2 generation in platelets as well as in plasma. Moreover, CuAsp significantly elevated the Pro level in plasma at the dose (10 mg·kg^{-1}) that inihibited the platelet aggregation and release. In contrast, Asp markedly lowered the Pro level in plasma while inhibited the TXA_2 formation. The reason that CuAsp significantly inhibited the TXA_2 generation might be its inhibitory effect on platelet cyclooxygenase. It is suggested that copper, an essential metalloelement, might be involved in the increased plasma levels of Pro in our present study.

On activation, platelets also release some vasoactive substances such as 5-HT, leading to further aggregation. In this study, CuAsp dose-dependently inhibited 5-HT release from platelets, suggesting that anti-platelet effects of CuAsp might

be related to its inhibitory action in the release of active substances from platelets.

In summary, as compared to Asp *in vitro* or *in vivo*, CuAsp was more potent in inhibiting AA-induced aggregation. Differing from Asp, CuAsp significantly increased the level of prostacyclin in plasma while it markedly decreased the generation of TXA_2 either in platelets or in plasma. This is advantageous to the prevention and therapy of ischemic cardiovascular diseases in combination with the abnormalities of platelet aggregation. Furthermore, CuAsp has much fewer side effects[2,4]. It is likely to become a more promising anti-platelet drug.

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阿司匹林铜的抗血小板聚集作用

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关键词 铜；阿司匹林；血小板聚集；血栓素 A_2；前列环素；5-羟色胺；花生四烯酸；腺苷二磷酸；血小板激活因子

目的：研究阿司匹林铜(CuAsp)对血小板聚集性的影响及其机制. **方法**：用 Born 氏法测定 CuAsp 对兔血小板聚集性的影响. 用荧光光度法和放射免疫法观察 CuAsp 对兔血小板 5-羟色胺的释放和 TXB_2 的产生及血浆中 TXB_2 和 6-keto-$PGF_{1\alpha}$水平的影响. **结果**：CuAsp 体外呈浓度依赖性抑制花生四烯酸(AA)诱导的血小板聚集和 5-羟色胺的释放(IC_{50}分别为 17 和 19 $\mu mol \cdot L^{-1}$，95 % 可信限为 9 - 33 和 10 - 30 $\mu mol \cdot L^{-1}$)，且抑制 TXB_2 的产生($P<0.05$). CuAsp 10 $mg \cdot kg^{-1}$灌胃选择性抑制 AA 诱导聚集. 降低血浆 TXB_2，同时升高 6-keto-$PGF_{1\alpha}$的水平($P<0.05$). **结论**：CuAsp 体内外均有比 Asp 更强的抗血小板聚集作用.