

- Physiol* 1974; 24 : 617
- 5 Hauswirth O, Singh BN. Ionic mechanisms in heart muscle in relation to the genesis and the pharmacological control of cardiac arrhythmias. *Pharmacol Rev* 1978; 30 : 5
 - 6 Manzanares J, Tamargo J. Electrophysiological effects of imipramine in non-treated and in imipramine-pretreated rat atrial fibres. *Br J Pharmacol* 1983; 79 : 167
 - 7 Goodman AG, Gilman LS. *The pharmacological basis of therapeutics*. 6th ed. NY: Macmillan, 1980: 762
 - 8 Isenberg G. Cardiac Purkinje fibres: the slow inward current component under the influence of modified $[Ca^{2+}]_i$. *Pflugers Arch* 1977; 371: 61
 - 9 Hoffman BF, Suckling EE. Effect of several cations on transmembrane potentials of cardiac muscle. *Am J Physiol* 1956; 186 : 317
 - 10 Hay DWP, Wadsworth RM. The effects of calcium channel inhibitors and other procedures affecting calcium translocation on drug-induced rhythmic contractions in the rat vas deferens. *Br J Pharmacol* 1983; 79 : 347

* * * * *

中国药理学报 *Acta Pharmacologica Sinica* 1989 Jul; 10 (4) : 342-345

达唑氧苯对麻醉兔脑血管阻力的作用¹

芮耀诚、孙笃新、龙 焜 (第二军医大学药理学系药理教研室, 上海 200433, 中国)

Effect of dazoxiben on cerebrovascular resistance in rabbits

RUI Yao-Cheng, SUN Du-Xin, LONG Kun (*Department of Pharmacology, Faculty of Pharmacy, Second Military Medical University, Shanghai 200433, China*)

ABSTRACT The effects of dazoxiben, a TXA_2 synthetase inhibitor, and indomethacin were compared on cerebrovascular resistance (CVR) and levels of serum TXB_2 , 6-keto-PGF_{1 α} (the stable metabolites of TXA_2 and PGI₂, respectively) and on protection from acute brain ischaemia caused by *ia* arachidonic acid (AA) in rabbits. The flow represented the cerebral blood flow (CBF) in two internal jugular arteries were measured with electromagnetic flow meter after occlusion of bilateral vertebral arteries and external jugular arteries. CVR was represented as blood pressure/(CBF·100 g brain). Serum TXB_2 and 6-keto-PGF_{1 α} levels were determined by radio-

immunoassay. The results showed that CVR and BP, EEG, ECG were not affected by treatment with *iv* dazoxiben 2 or 10 mg/kg. The CVR was enhanced by 35.5 and 49.8% at 30 and 40 min, respectively after *iv* indomethacin 10 mg/kg. The serum TXB_2 level (872 ± 85) was inhibited to 511 ± 169 pg/ml ($n=5$, $P<0.05$) and 6-keto-PGF_{1 α} increased from 668 ± 309 to 890 ± 357 pg/ml ($n=5$, $P<0.05$) at 30 min after *iv* 2 mg/kg dazoxiben. However, both TXB_2 and 6-keto-PGF_{1 α} decreased by 26.4 and 32.7%, respectively at 40 min after *iv* indomethacin 10 mg/kg. In a model of cerebral ischaemia caused by *ia* AA in rabbits, the EEG change and enhancement of CVR were antagonized by *iv* dazoxiben 10 mg/kg completely, but only partly antagonized by indomethacin 10 mg/kg. The

Received 1988 Jul 23 Accepted 1988 Dec 28

¹Project supported by the Shanghai Science and Technology Developing Foundation № 863430906

results suggest that PGI_2 and TXA_2 may play a minor role in the regulation of CVR in the physiological condition. When the cyclooxygenase pathway of arachidonate metabolism is inhibited by indomethacin 10 mg/kg, the leukotrienes (LTs) which are the products of 5-lipoxygenase metabolites of AA may release so and thus CVR is enhanced. In comparison of two types of arachidonate metabolism inhibitors, the TXA_2 synthetase inhibitor is better in the treatment of brain ischaemia.

KEY WORDS dazoxiben; vascular resistance; thromboxane A_2 ; thromboxane synthetase; indomethacin; thromboxane B_2 ; 6-ketoprostaglandin $\text{F}_{1\alpha}$

摘要 麻醉兔 iv 达唑氧苯 2, 10 mg/kg, 对基础脑血管阻力(CVR)及脑电图(EEG), 血压(BP)等无显著影响, 血浆 TXB_2 水平显著降低, 6-keto- $\text{PGF}_{1\alpha}$ 显著升高。吲哚美辛 10 mg/kg iv 使 CVR 升高, 血浆 TXB_2 和 6-keto- $\text{PGF}_{1\alpha}$ 降低。达唑氧苯 10 mg/kg 能显著对抗椎动脉内注射 AA 引起的 CVR 增加, 而相同剂量的吲哚美辛不能完全对抗。提示 TXA_2 合成酶抑制剂在脑缺血的应用中有益。

关键词 达唑氧苯; 血管阻力; 血栓素 A_2 ; 血栓素合成酶; 吲哚美辛; 血栓素 B_2 ; 6-酮前列腺素 $\text{F}_{1\alpha}$

脑缺血时花生四烯酸(AA)环氧酶代谢产物——血栓素(TXA_2)释放增加⁽¹⁾。 TXA_2 是强的血小板聚集剂和血管收缩剂, 选择性 TXA_2 合成酶抑制剂抑制 TXA_2 释放, 有益于前列环素(PGI_2)生成, 对某些栓塞性外周血管病有一定疗效, 对脑血管病的应用研究正在进行^(2,3)。环氧酶抑制剂如吲哚美辛(indomethacin)降低基础脑血流量及 CO_2 反应性血流量的增加, 对脑缺血的作用尚无一致意见^(4,5)。本实验比较 TXA_2 合成酶抑制剂达唑氧苯(dazoxiben, UK 37248)和吲哚美辛对兔脑血管阻力的影响及其与血浆中 TXB_2 , 6-keto- $\text{PGF}_{1\alpha}$ 水平变化的关系, 以及对 AA 引起的脑血管痉挛的保护作用。

MATERIALS AND METHODS

材料 达唑氧苯由我系有机教研室合成, 生理盐水配成所需浓度; 吲哚美辛为上海十七制药厂生产; AA-Na(99%)为 Sigma 公司产品; TXB_2 , 6-keto- $\text{PGF}_{1\alpha}$ 放射免疫测定盒购自北京协和医科大学基础部药理室; New Zealand 兔由本校动物所提供。

基础脑血管阻力的测定 New Zealand 兔, ♂, 体重 $2.91 \pm \text{SD } 0.19 \text{ kg}$, 分为对照组, 达唑氧苯 2, 10 mg/kg 组及吲哚美辛 10 mg/kg 组。耳 iv 20% 乌拉坦 1 g/kg 麻醉, 仰位固定, 气管插管, 一侧股动脉插管至腹主动脉测动脉压(BP), 股静脉插管供给药。在颈根部分离并结扎二侧椎动脉, 再结扎二侧颈外动脉及其分支⁽⁶⁾, 二侧颈总动脉分别放置直径适宜的电流量计探头(1-2 mm), 连接于 MFV-1200 型电流量计上, 测量两侧颈内动脉血流量(ml/min), 它们之和代表全脑血流量(CBF)⁽⁷⁾。记录额一顶叶脑电图(EEG)及 II 导联心电图及心率(HR)。上述指标均同步记录于 RM-6000 型多道生理记录仪上。

手术开始后 iv 肝素 1000 U/kg, 各项指标于术毕 30 min 后开始记录。记录给药前及给药后 5, 10, 30, 40 min 各项指标的变化。实验结束后, 取出全脑称重, 计算脑血管阻力(CVR)⁽⁸⁾, 其公式: $\text{BP}(\text{kPa}) / [\text{CBF}(\text{ml}/\text{min}) \cdot 100 \text{ g brain}]$ 。

血浆中 TXB_2 , 6-keto- $\text{PGF}_{1\alpha}$ 的测定 血浆中 TXA_2 和 PGI_2 的稳定代谢产物分别为 TXB_2 , 6-keto- $\text{PGF}_{1\alpha}$, 用放射免疫法测定 TXB_2 和 6-keto- $\text{PGF}_{1\alpha}$ 表示 TXA_2 和 PGI_2 的量的变化, 给药前及给药后 5, 10, 30, 40 min 分别从动脉取血 2 ml, 按文献⁽⁹⁾制备血浆 1 ml, 经乙醚处理后, 重蒸醋酸乙酯提取 2 次, N_2 气下吹干, 置 -40°C 冰箱内备用。

对椎动脉内注射 AA 引起急性脑缺血的保护作用 New Zealand 兔, ♂, 体重 $2.2 \pm 0.4 \text{ kg}$, 分为对照组(生理盐水 0.5 ml/kg), 达唑

氧苯(10 mg/kg)及吲哚美辛(10 mg/kg) 3组。乌拉坦麻醉后,结扎两侧颈外动脉及左侧椎动脉,右侧锁骨下动脉在结扎除椎动脉外的所有分支后,插管供给药用。电磁流量计测两侧颈内动脉血流量,与前述方法相同。

各项指标稳定后给药,10 min后从椎动脉内注射(ia)AA-Na溶液0.1 mg(0.1 ml),每隔5 min注射一次,共四次,观察注射后30,60 min CVR, EEG等指标的变化⁽¹⁰⁾。

RESULTS

对基础脑血管阻力的影响(Tab 1)。达唑氧苯2,10 mg/kg对脑血管阻力无明显影响,对HR, ECG, BP, EEG也无明显影响。吲哚美辛10 mg/kg给药后30, 40 min脑血管阻力分别增加35.5, 49.8%,与给药前相比P均<0.05。给药前BP为13.6±1.5, 给药后, 5, 10 min分别为15.1±1.6 (11%), 15±1.7 (11%)kPa, 10 min后逐渐恢复至正常, 给药前HR为258±39 bpm, 给药后5, 10, 30, 40 min分别为242±34, 242±32, 241±34, 238±44 bpm, 改变不明显。

对血中TXB₂, 6-keto-PGF_{1α}的影响(Tab 1)。达唑氧苯2, 10 mg/kg给药5 min可使血浆TXB₂水平显著下降, 40 min时分别下降34.5及37.8%(P<0.01)。两剂量下降幅度之间没有明显差别。对血浆6-keto-PGF_{1α}, 达唑氧苯2 mg/kg给药后30, 40 min分别升高33.3及44.3%,较给药前升高显著(P<0.05), 10 mg/kg升高39.2及43.7%(P<0.05)。两剂量组间无显著差异。吲哚美辛10 mg/kg给药后30, 40 min使血浆中TXB₂水平下降28.3及26.4%(P<0.05)。

对AA引起急性脑缺血的保护作用(Tab 2)。对照组AA椎动脉内注射后30 min, EEG振幅明显变小, 60 min后5只兔中4只几乎变平或平坦, CVR于30 min后明显增加, 与EEG变化一致。达唑氧苯10 mg/kg iv对AA引起的CVR升高有显著对抗作用, 其CVR与ia AA前相近。EEG 5只兔中仅1只变小, 其余4只未见明显变化, 而2 mg/kg无保护作用。吲哚美辛10 mg/kg对3只兔EEG无明显影响, 另2只明显减小, 对AA引起的CVR升高无对抗作用。

Tab 1. Effect of dazoxiben on cerebrovascular resistance (R, kPa/(ml/min)·100 g brain) and the levels of TXB₂ (T, pg/ml plasma), 6-keto-PGF_{1α} (P, pg/ml plasma) in rabbit. $\bar{x} \pm SD$. *P>0.05, **P<0.05, ***P<0.01.

Drug (mg/kg)	n	Time after medication (min)				
		0	5	10	30	40
Control						
(R)	8	0.091±0.028	0.091±0.037*	0.088±0.033*	0.096±0.031*	0.101±0.043*
(T)	6	795±283	727±202*	715±225*	688±181*	919±179*
(P)	7	885±304	947±225*	875±182*	866±152*	874±224*
Dazoxiben						
2 (R)	8	0.098±0.045	0.096±0.045*	0.099±0.048*	0.119±0.052*	0.107±0.052*
(T)	5	872±85	608±102**	696±38**	511±169**	571±64***
(P)	5	668±309	732±244*	788±244*	890±357**	963±349**
10 (R)	6	0.101±0.025	0.098±0.027*	0.099±0.027*	0.108±0.033*	0.109±0.031*
(T)	6	1031±433	797±464**	752±304**	925±426**	617±353***
(P)	7	837±207	1060±391*	961±277**	1165±433**	1190±362**
Indomethacin						
10 (R)	7	0.088±0.021	0.107±0.067*	0.123±0.073*	0.119±0.041**	0.132±0.044**
(T)	6	728±107	609±185*	610±216*	520±200**	536±106***
(P)	6	1047±254	768±239**	820±101**	720±313**	705±243***

Tab 2. Effect of dazoxiben on the cerebrovascular resistance [kPa/(ml/min)·100 g brain] after ia arachidonic acid. n=5. $\bar{x} \pm SD$. * $P > 0.05$, ** $P < 0.05$, *** $P < 0.01$.

Drug (mg/kg)	Time after ia AA 0.4 mg(min)		
	0	30	60
Control	0.096 ± 0.023	0.115 ± 0.019**	0.128 ± 0.017***
Dazoxi- ben 10	0.081 ± 0.027	0.081 ± 0.020*	0.084 ± 0.023*
Indome- thacin 10	0.092 ± 0.035	0.101 ± 0.037***	0.108 ± 0.041***

DISCUSSION

本研究表明 TXA₂ 合成酶抑制剂达唑氧苯 2, 10 mg/kg 虽可使血浆 TXA₂ 水平显著降低, PGI₂ 显著升高, 但对基础脑血管阻力并无显著影响。提示在生理情况下, 脑血管阻力的调节中, TXA₂ 与 PGI₂ 可能不起主要作用, 或其作用甚微。吲哚美辛 10 mg/kg 使血浆 TXB₂ 和 6-keto-PGF_{1α} 水平均显著降低, CVR 增高。从理论上当环氧酶受到抑制后, AA 脂氧酶代谢途径增强, 白三烯(LT₄)释放增加, 已知 LT₄ 为强血管收缩剂, 可能为增高 CVR 的原因。此结果与环氧酶抑制剂在较大剂量时使基础脑血流量减少的报道⁽⁵⁾一致。

AA 为血小板强的聚集剂, 能产生栓塞, 这种血小板聚集作用可能由于 AA 代谢形成的前列腺素类物质(PG₂), 包括前列腺素内过氧化物(PGG₂, PGH₂)和 TXA₂ 等, 这些代谢物除引起血小板聚集外, 还可引起脑血管收缩。椎动脉内注射 AA 可引起急性脑缺血, 表现在 CVR 升高, EEG 幅度降低至平坦, 达唑氧苯能完全对抗 AA 引起的脑缺血, 同时对 BP, HR 等血流动力学指标无明显不良影响。吲哚美辛能部分对抗 AA 引起的 EEG 变化, CVR 升高程度也较对照组稍小, 但无显著差异, 可能由于 AA 代谢产物的生成部分受到抑制。两类药物相比, 在脑缺血的防治中达唑氧苯优于环氧酶抑制剂。

达唑氧苯减少血浆 TXA₂ 水平, 可部分解释其对抗 AA 的缩血管作用机理。近年来发现 TXA₂ 合成酶抑制剂能有效阻止 LTD₄ 引起的豚鼠支气管收缩⁽¹¹⁾, 其对脑血管是否也有类似作用, 正在进一步研究, 以期阐明达唑氧苯保护 AA 引起缺血的机理。

REFERENCES

- 1 Shohami E, Rosenthal J, Lavy S. The effect of incomplete cerebral ischemia on prostaglandin level in rat brain. *Stroke* 1982; 13 : 494
- 2 Ellis EF, Nies AS, Oates JA. Cerebral arterial smooth muscle contraction by thromboxane A₂. *Ibid* 1977; 8 : 480
- 3 Yamazaki H, Fujimoto T, Suzuki H, Tanoue K. Vasospasm and injuries of cerebral arteries induced by activation of platelets in vivo: it may be due to thromboxane A₂. *Adv Prostaglandin Thromboxane Leukotriene Res* 1985; 15 : 469
- 4 Harris RJ, Bayhan M, Branstom NM, Watson A, Symon L. Modulation of the pathophysiology of primate focal cerebral ischaemia by indomethacin. *Stroke* 1982; 13 : 17
- 5 Wennmalm A, Carlsson I, Edlund A, Eriksson S, Kaljser L, Nowak J. Central and peripheral hemodynamic effects of non-steroidal antiinflammatory drugs in man. *Arch Toxicol* 1984; 7 (Suppl): 350
- 6 Sun QX, Chen WZ, Li HY, Ting KS. Studies on antibilharzial drugs. XV. Effect of tartar emetic on the cerebral blood flow in rabbits. *Acta Physiol Sin* 1959; 23 : 29
- 7 Piper PJ, Stanton AWB. Leukotrienes and the intracranial circulation. *Adv Prostaglandin Thromboxane Leukotriene Res* 1985; 15 : 333
- 8 Meyer JS, Ishikawa S, Lee TK. Electromagnetic measurement of internal jugular venous flow in the monkey. *J Neurosurg* 1964; 21 : 524
- 9 Wang Z, Zhu GQ, Huang RS, An Y, Cheng JX, Liu JS. Radioimmunoassay for thromboxane B₂. *Acta Acad Med Sin* 1986; 8 : 139
- 10 Okamoto S, Peck RC, Lefer AM. Protective actions of dexamethasone in acute cerebral ischemia. *Circ Shock* 1982; 9 : 445
- 11 Muccitelli RM, Osborn RR, Weichman BM. Effect of inhibition of thromboxane production on the leukotriene D₄-mediated bronchoconstriction in the guinea pig. *Prostaglandins* 1983; 26 : 197