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Effect of clobenpropit on regional cerebral blood flow in rat hippocampus[1]

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KEY WORDS clobenpropit; histamine H_3 receptors; metoprine; methylhistamines

ABSTRACT

AIM: The effect of clobenpropit on regional cerebral blood flow (rCBF) was investigated in the rat hippocampus. **METHODS**: rCBF was determined in the hippocampus by the hydrogen clearance method. The blood pressure was measured by a tail-cuff plethysmograph. **RESULTS**: Intracerebroventricular (icv) injection of clobenpropit (20, 50 μg), a representative H_3-antagonist, dose-dependently and significantly increased rCBF in the hippocampus. The increase of rCBF induced by clobenpropit was enhanced by metoprine (1, 2 mg/kg), a selective histamine *N*-methyltransferase inhibitor; however, was antagonized by an H_3-agonist, (R)-α-methylhistamine (5 μg), an H_1-antagonist, mepyramine (5 - 10 mg/kg), and an H_2-antagonist, zolantidine (10 mg/kg). Clobenpropit caused no apparent effects on blood pressure even at a high dose of 50 μg. **CONCLUSION**: These results suggest that brain endogenous histamine may contribute to increase rCBF in the rat hippocampus via both the post-synaptic H_1-, H_2-receptors and the pre-synaptic H_3-receptor.

INTRODUCTION

It has been found that the increase in brain histamine upregulates central excitatory activity[1] and awaking[2], and the decrease in histamine prolongs the phase of convulsions[3]. In our previous studies, it was observed that icv injection of histamine facilitates memory process in rats[4-6], while depletion of histamine impairs both avoidance response and radial maze learning[7]. In addition to these studies, we preliminarily reported that icv injection of histamine could increase the regional cerebral blood flow (rCBF) in the hippocampus mediated by both H_1- and H_2-receptors[8]. However, whether pre-synaptic H_3-receptor was involved or not in regulating rCBF has not yet been reported.

Pre-synaptic histamine H_3-receptors are generally known to control both synthesis and release of neuronal histamine[9,10]. Clobenpropit, a representative H_3-antagonist, is reported to activate the central histaminergic system enhancing histamine synthesis and release from nerve terminals[11-13], and is now widely regarded as a new tool to study precise central endogenous histamine functions, wherein it is reported to ameliorate the memory process and locomotor memory[11,12].

Therefore, the present study was designed to clarify the age-dependent effect of clobenpropit on rCBF in the rat hippocampus.

MATERIALS AND METHODS

Animals Wistar rats (♂, 2 - 16 months old, Charles River, Tokyo, Japan, $n = 55$), maintained in individual cages with a 12-h light-dark cycle (lights on from 8:00 - 20:00) were used. Water was given *ad libitum*. Experiments were carried out each day between 12:00 - 19:30.

Surgical procedure Rats were anesthetized with sodium pentobarbital (35 mg/kg, ip), and fixed on a stereotaxic apparatus (Narishige, SR-5, Tokyo, Japan). Polyurethane-coated platinum/platinum black electrode (300 μm in diameter, Unique Medical, Tokyo, Japan) was implanted into the hippocampus (AP: -4.3 mm, L: 1.8 mm, H: 3.5 mm) according to the following coordinates measured from bregma[14]. Electrodes were connected to a miniature receptacle placed on the skull and fixed with dental cement. In addition, a guide cannula made of stainless steel tubing 700 μm in outer diameter, was implanted into the right lateral ventricle (AP: -0.9 mm, L: 1.5 mm, H: 3.8 mm). At least 14 d

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were allowed for recovery from the surgery.

Measurement of rCBF rCBF in the hippocampus was determined by hydrogen clearance methods with a digital UH meter (Unique Medical, Model MHG-D1, Tokyo, Japan) as described previously[8,15,16]. In short, hydrogen was administered to the animals by inhalation for 30 s. The time ($T_{1/2}$) required to reduce the original level by half on the clearance curve was measured and the rCBF ($mL \cdot min^{-1} \cdot kg^{-1}$) was estimated. After experiments, all rodents were sacrificed by decapitation, and implantation of electrode was checked by histopathological analysis. Fifteen of 55 rats in which implantation of electrode was uncorrect or infection was observed around the electrode, were excluded.

Measurement of mean blood pressure Blood pressure was measured[8] using a tail-cuff plethysmograph (Softron, BP-98A, Softron, Tokyo, Japan) after prewarming the rats for 10 min at 37 ℃.

Drugs Clobenpropit dihydrobromide (kindly provided by Prof Timmerman, Leiden-Amsterdam Center for Drug Research, Vrije Universiteit Amsterdam, the Netherlands) and (*R*)-α-methylhistamine (donated by Prof Schwartz, Unite de Neurobiologie et Pharmacologie, Centre Paul Broca, Paris, France) were dissolved in saline and injected icv in a fixed volume of 5 μL over a period of 60 s at a constant speed with a continuous infusion pump (KN-201, Natsume, Tokyo, Japan), and metoprine (a gift from Dr Nichol, Wellcome Research Laboratories, Research Triangle Park, NC), mepyramine maleate (Sigma, St Louis, MO, USA), and zolantidine dimaleate (SmithKline Beecham, London, UK) dissolved in saline, were injected ip. Studies for drug effect were carried out twice a week, on Tuesdays and Fridays. The same animals were repeatedly used, and they experienced all doses of either drugs administered in an ascending order.

Statistics One-way analysis of variance with Dunnett's test was used for calculating a significant difference. Values are shown as $\bar{x} \pm s$.

RESULTS

Age-dependent effect of clobenpropit on the rCBF in rat hippocampus As shown in Fig 1, ip injection of clobenpropit (50 μg) increased rCBF in the hippocampus among 2 – 16-month-old rats. In addition, in the saline control group, rCBF in the hippocampus decreased gradually with age, and a stable and significant decrease in rCBF was found in rats from 8 – 16 months of age.

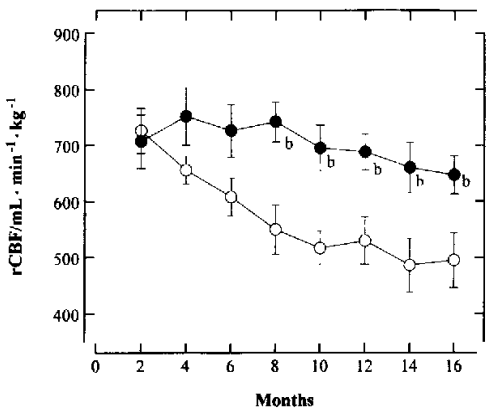

Fig 1. Age-dependent effects of icv injection of clobenpropit on rCBF in the rat hippocampus. (○) **saline (icv),** (●) **Clobenpropit (icv).** $n = 8$ **rats.** $\bar{x} \pm s$. $^bP < 0.05$ *vs* **saline-treated group.**

Effects of clobenpropit and (R)-α-methylhistamine on the rCBF in rat hippocampus Icv injection of clobenpropit increased rCBF in the hippocampus, dose-dependently. At doses of 5 and 10 μg clobenpropit showed no marked effect, while at doses of 20 and 50 μg it caused a significant increase in rCBF at 15 – 30 min, and with a peak time of 30 min ($P < 0.05$). As shown in Tab 1, (*R*)-α-methylhistamine, a representative H_3-agonist, reversed clobenpropit-induced increase in rCBF in a dose-dependent manner, and a significant effect was observed at a dose of 5 μg ($P < 0.05$).

Effect of H_1- and H_2-antagonist on clobenpropit-induced increase in rCBF in rat hippocampus H_1-antagonist, mepyramine, reduced clobenpropit-induced increase in rCBF dose-dependently, and a significant effect was observed at doses of 5 and 10 mg/kg ($P < 0.05$, Tab 2). Similar to mepyramine, H_2-antagonist, zolantidine, also markedly reversed clobenpropit-induced increase in rCBF at a dose of 10 mg/kg ($P < 0.05$).

Effect of clobenpropit in combination with metoprine on rCBF in rat hippocampus As shown in Tab 3, pretreatment with metoprine (1, 2 mg/kg) 3.5 h before clobenpropit administration significantly potentiated the increase in rCBF induced by 5 and 10 μg of clobenpropit ($P < 0.05$) at the doses which caused no appreciable change when given alone (Tab 2). On the other hand, metoprine resulted in an increase in rCBF in hippocampus, however no significant effects were observed,

Tab 1. Effect of clobenpropit on the rCBF in the rat hippocampus. RAHA: (R)-α-methylhistamine. RAHA or saline were given simultaneously with clobenpropit. $n = 8$ rats. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* saline-treated group. $^eP < 0.05$ *vs* clobenpropit (50 μg) + saline-treated group.

Drugs	Dose/μg (icv)	rCBF/mL·min^{-1}·kg^{-1} 0 min	5 min	15 min	30 min	60 min	90 min	120 min
Saline		524 ± 30	500 ± 29	529 ± 31	495 ± 22	512 ± 36	504 ± 26	514 ± 28
Clobenpropit	5	532 ± 33	545 ± 49	560 ± 30	538 ± 31	538 ± 29	495 ± 42	527 ± 30
	10	522 ± 28	562 ± 52	591 ± 35	593 ± 30	557 ± 26	529 ± 34	520 ± 33
	20	525 ± 35	609 ± 37	648 ± 38	682 ± 44^b	620 ± 35	538 ± 25	519 ± 29
	50	520 ± 31	656 ± 44	702 ± 47^b	734 ± 53^c	661 ± 50	576 ± 33	536 ± 43
Clobenpropit + Saline	50	524 ± 45	629 ± 52	693 ± 55	726 ± 62	656 ± 54	584 ± 40	555 ± 48
Clobenpropit + RAHA	50							
	1	532 ± 29	650 ± 51	686 ± 47	689 ± 49	632 ± 29	590 ± 45	546 ± 28
	2	529 ± 32	633 ± 40	605 ± 53	567 ± 61	605 ± 46	572 ± 36	534 ± 44
	5	536 ± 37	606 ± 42	550 ± 34^e	529 ± 55^e	560 ± 38	526 ± 40	523 ± 31
RAHA	1	522 ± 49	504 ± 54	500 ± 40	488 ± 45	505 ± 46	519 ± 45	516 ± 38
	2	508 ± 35	490 ± 47	506 ± 55	519 ± 50	523 ± 48	514 ± 31	516 ± 33
	5	519 ± 37	513 ± 42	485 ± 38	508 ± 43	506 ± 48	512 ± 56	530 ± 44
	10	527 ± 40	506 ± 53	487 ± 46	480 ± 51	500 ± 57	514 ± 38	523 ± 40

Tab 2. Effect of H_1- and H_2-antagonists on clobenpropit-induced increase in rCBF in the rat hippocampus. $n = 8$ rats. $\bar{x} \pm s$. $^bP < 0.05$ *vs* clobenpropit + saline-treated group.

Drugs	Dose	rCBF/mL·min^{-1}·kg^{-1} 0 min	5 min	15 min	30 min	60 min	90 min	120 min
Clobenpropit + Saline	50 μg, icv	526 ± 32	649 ± 45	700 ± 43	728 ± 50	671 ± 47	580 ± 35	531 ± 42
Clobenpropit + Mepyramine	50 μg, icv							
	2 mg/kg, ip	535 ± 30	639 ± 37	630 ± 25	633 ± 50	616 ± 34	558 ± 32	524 ± 36
	5 mg/kg, ip	538 ± 27	580 ± 49	564 ± 46	552 ± 43^b	585 ± 45	560 ± 29	519 ± 30
	10 mg/kg, ip	520 ± 35	572 ± 42	548 ± 58	529 ± 54^b	620 ± 35	538 ± 25	527 ± 23
Clobenpropit + Zolantidine	50 μg, icv							
	2 mg/kg, ip	521 ± 40	612 ± 33	671 ± 35	660 ± 46	627 ± 45	542 ± 34	520 ± 33
	5 mg/kg, ip	532 ± 37	625 ± 40	577 ± 38	570 ± 57	538 ± 29	495 ± 47	527 ± 30
	10 mg/kg, ip	528 ± 29	599 ± 24	552 ± 27^b	545 ± 50^b	562 ± 36	554 ± 26	534 ± 28

even at a high dose of 10 mg/kg.

Effect of clobenpropit on mean blood pressure Icv injection of clobenpropit resulted in no appreciable changes in mean blood pressure even at a high dose of 50 μg from 0 to 180 min after injection (Tab 4).

DISCUSION

In the present study, it was found that clobenpropit significantly increased rCBF in hippocampus. It is generally known that H_3-receptors regulate the synthesis and release of neuronal histamine, and clobenpropit is a specific and potent H_3-antagonist[12,13], and is now widely regarded as a tool to study central endogenous histamine function[11-13,17]. Kakinoki *et al*[3] found that brain endogenous histamine content was decreased by icv injection of clobenpropit and thioperamide. We have previously found that (data not shown), clobenpropit (20, 50 μg) alone tends to decrease histamine contents in the hippocampus and cortex, and dose-dependently and significantly decreases histamine contents induced by α-fluoromethylhistidine, which is well known as a selective inhibitor of histidine decarboxylase. It is well known that α-fluoromethylhistidine markedly decreases endogenous histamine content from the nerve terminals without affecting the levels of other neurotransmitters[7]. These results suggest that clobenpropit enhances endogenous histamine release. Therefore, the reason why clobenpropit increased

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Tab 3. Effect of clobenpropit in combination with metoprine on rCBF in the rat hippocampus. $n = 8$ rats. $\bar{x} \pm s$. $^bP < 0.05$ *vs* metoprine (1 mg/kg) + saline-treated group. $^eP < 0.05$ *vs* metoprine (2 mg/kg) + saline-treated group.

Drugs	Dose	rCBF/mL·min^{-1}·kg^{-1} 0 min	5 min	15 min	30 min	60 min	90 min	120 min
Saline	ip	532 ± 41	524 ± 30	509 ± 25	498 ± 36	517 ± 36	514 ± 37	528 ± 29
Metoprine	1 mg/kg, ip	520 ± 31	526 ± 41	530 ± 44	541 ± 31	523 ± 51	526 ± 30	525 ± 42
	2 mg/kg, ip	522 ± 29	534 ± 43	545 ± 34	540 ± 38	543 ± 29	529 ± 41	512 ± 36
	5 mg/kg, ip	515 ± 22	547 ± 42	554 ± 43	570 ± 44	548 ± 33	538 ± 24	535 ± 30
	10 mg/kg, ip	518 ± 35	570 ± 64	588 ± 51	615 ± 54	590 ± 45	563 ± 29	552 ± 41
Metoprine + Saline	1 mg/kg, ip ip	528 ± 40	526 ± 41	535 ± 47	538 ± 45	517 ± 54	523 ± 42	520 ± 42
Metoprine + Clobenpropit	1 mg/kg, ip 5 μg, icv	520 ± 38	599 ± 27	628 ± 36	642 ± 33	640 ± 35	534 ± 29	536 ± 25
	10 μg, icv	514 ± 30	656 ± 44	681 ± 49	704 ± 49^b	670 ± 45	590 ± 44	543 ± 40
Metoprine + Saline	2 mg/kg, ip ip	525 ± 40	522 ± 48	549 ± 43	537 ± 50	547 ± 32	526 ± 47	519 ± 44
Metoprine + Clobenpropit	2 mg/kg, ip 5 μg, icv	525 ± 35	609 ± 37	658 ± 33	691 ± 47^e	667 ± 34	598 ± 22	542 ± 35
	10 μg, icv	520 ± 31	675 ± 46	722 ± 47^e	746 ± 55^e	699 ± 40^e	616 ± 33	550 ± 33

Tab 4. Effect of clobenpropit on mean blood pressure in rats. $n = 8$ rats. $\bar{x} \pm s$.

Drugs	Dose/μg (icv)	Mean blood pressure/mmHg 0 min	5 min	15 min	30 min	60 min	90 min	120 min
Saline		110 ± 3	112 ± 3	111 ± 4	109 ± 3	109 ± 3	112 ± 2	109 ± 3
Clobenpropit	5	109 ± 3	114 ± 4	114 ± 4	113 ± 3	111 ± 3	112 ± 4	110 ± 3
	10	109 ± 3	113 ± 5	114 ± 3	113 ± 3	112 ± 2	113 ± 3	113 ± 3
	20	111 ± 4	115 ± 4	113 ± 3	114 ± 4	112 ± 4	111 ± 2	109 ± 3
	50	111 ± 3	114 ± 4	114 ± 5	112 ± 5	110 ± 3	112 ± 3	110 ± 4

rCBF in the hippocampus in the present study, may be that, clobenpropit promoted the release of hippocampal endogenous histamine from histaminergic pre-synaptic terminals, and the released histamine was effective to increase rCBF in the hippocampus. In addition, it has been reported that rCBF in the cortex reduces in stroke prone spontaneously hypertensive rats with severe hypertension, however, in our study, the treatment of clobenpropit resulted in no appreciable change of blood pressure even at a high dose of 50 μg, therefore, it is likely that clobenpropit-induced increase in rCBF was unrelated to blood pressure.

Moreover, in this study, the effect of clobenpropit was potentiated by metoprine, a selective inhibitor of histamine N-methyltransferase[18], reported to potentiate the thioperamide-induced histamine release[19]. Thioperamide is another potent H_3-antagonist[9,10,12]. Therefore, by inhibiting the metabolism of histamine released by clobenpropit, and enhancing clobenpropit-induced histamine release, metoprine potentiates clobenpropit-induced increase in rCBF. The present findings strongly support our previous hypothesis[8] that brain histamine increases the rCBF in the hippocampus. However, metoprine alone creates no appreciable effect on rCBF, even as it is found to increase brain histamine contents in a manner similar to histidine[3,20]. Tuominen *et al* reported that metoprine could not affect the secretion of prolactin the same as histidine, and therefore suggested that metoprine may be not suitable as a tool to elevate endogenous histamine[20].

It was also observed in the present study that the clobenpropit-induced increase in rCBF in the hippocampus was markedly blocked by (*R*)-α-methylhistamine, a representative and highly selective H_3-agonist in a dose-dependent manner[10,12]. This observation strongly suggests that the effects of clobenpropit are mediated through

the auto-receptors located on histaminergic neurons. In addition, the increased rCBF in the hippocampus induced by clopenpropit was reversed by both mepyramine and zolantidine, the representative H_1- and H_2-antagonists, respectively. It has been reported that H_2-receptors exist widely in smooth muscle cell layer of intracerebral arterioles, and both H_1 and H_2-receptor in the inner smooth muscle[21]. Extraluminally administered histamine resulted in a dose-dependent vasodilation of isolated intracerebral arterioles, and its effect was blocked by both cimetidine and chlorpheniramine[22]. The present results are in support of the previous study[8,21], in which it was found that icv injection histamine or H_1- and H_2-agonist resulted in an increase of rCBF in the hippocampus, probably by vasodilating cerebral arterioles in the hippocampus.

On the other hand, it has been reported that H_3-receptor also is a heteroreceptor located on non-histaminergic neurons, and many evidences indicate that stimulation of H_3-receptors can also regulate the release of acetylcholine, noradrenaline, dopamine, serotonin[10,12,23], which are involved in the regulation of rCBF[24,25]. Therefore, clobenpropit-induced release of these transmitters may also play an important role in the observed increase of rCBF in the hippocampus. In conclusion, histamine may play a certain role in regulating rCBF in the rat hippocampus, and its action is involved in both presynaptic H_3-receptor and post-synaptic H_1- and H_2-receptors.

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Clobenpropit 改善大鼠海马局部脑血流的作用[1]

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关键词 clobenpropit; 组胺 H_3 受体; 氯苯氨啶; 甲基组胺类

目的: 研究和阐明 clobenpropit 对大鼠海马局部脑血流(rCBF)的作用机制. **方法**: 采用氢清除法测定海马的局部脑血流, 并利用大鼠尾部体积描记器测定大鼠的血压. **结果**: 侧脑室内注射 clobenpropit(20, 50 μg)后, 15 - 30 min, 可剂量依赖性、显著地改善 8 - 16 月龄大鼠海马中的 rCBF, 而且 clobenpropit 的作用可被氯苯氨啶加强. (R)-α-甲基组胺(5 μg)则明显抑制 clobenpropit 的 rCBF 改善作用. 另外, 美吡拉敏 (5, 10 mg/kg)和 zolantidine (10 mg/kg)均可剂量依赖性地抑制 clobenpropit 提高 rCBF 的作用. Clobenpropit (5 - 50 μg)对血压不产生影响. **结论**: Clobenpropit 可以改善 8 - 16 月龄大鼠海马中 rCBF, 其作用主要与组胺 H_1, H_2 和 H_3 受体相关.

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