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The Effect of Intraventricular Injection of Tolazoline on PGE_1-Induced Fever in the Rabbit

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Abstract: The interactions of prostaglandin E_1 (PGE_1) and tolazoline, as well as noradrenaline (NA) and dipyron on fever induction were studied in rabbits through intraventricular microinjection technique. Monitorings of febrile responses were made on rectal temperature, ear skin temperature and respiratory frequency. Pre-injected tolazoline, an alpha-adrenoceptor blockade diminished febrile responses elicited by PGE_1, whereas post-injected tolazoline didn't induce any antagonistic effects on PGE_1-fever, rather it facilitated febrile responses, especially drop of ear skin temperature, or in a few cases it induced shivering. Tolazoilne is the antagonist of both alpha 1-and alpha 2-adrenoceptors and also the weak antagonist for 5-hydroxytryptamine (5-HT). So it is assumed that post-injected tolazoline may not act on the receptor sites on which PGE_1 has already occupied, and would inhibit other receptors which are responsible for the antagonism of fever induction, *ie* the facilitation of warm responsive units or the inhibition of cold responsive units. An antipyretic drug dipyron was antagonistic to all the responses elicited by PGE_1 and NA. It also depressed febrile responses exaggerated by tolazoline. Considering the presynaptic inhibitory modulation of PGE_1, the results would permit us to conclude that PGE_1 may act on presynaptic alpha 2-adrenoceptor which modulate synaptic transmission onto cold responsive units, and the effect of dipyron might be involved in such synaptic transmission.

Key words: Prostaglandin E_1, Noradrenaline, Tolazoline, Dipyron, Alpha-adrenoceptor, Presynaptic modulation

INTRODUCTION

Since 1970, many authors have reported the potent pyrogenesity of PGE_1 and PGE_2 in various species such as rats (Siren, 1982), rabbits (Feldberg and Saxena, 1971; Milton and Wendlandt, 1970; Stitt, 1973), cats (Siren, 1982), sheep (Bligh and Milion,

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1973; Hales *et al.*, 1973). In '60s, however, it was believed that biogenic amines regulate body temperature, and thus roles of noradernaline (NA), 5-hydroxytryptamine (5-HT) and acetylcholine (ACh) were intensively studied. It is of great interest that experiments of amine-administration in various species provided discordant results depending on each species. For example, rabbits became hyperthermic in response to cerebroventricular injection of NA (Bligh *et al.*, 1971; Cooper *et al.*, 1965), but cats (Feldberg and Myers, 1964) and monkeys (Myers and Yaksh, 1969) became hypothermic in response to NA, while rats were hyperthermic (Myers and Yaksh, 1968), hypothermic (Cantor and Satinoff, 1976), or both (Lin *et al.*, 1980). Differently to these evidences, PGEs equally induce fever in these animals. Thus some investigators have studied the relationship between PGE_1 and these amines especially NA, using adrenoceptor bocking agents (Laburn *et al.*, 1975; Lin *et al.*, 1982). The hypothesis resulted from the studies was that, PGE_1 would induce the releases of NA (Laburn *et al.*, 1975) which acts on the adrenoceptor of cold signal-travelling pathway or PGE_1 might directly act on adrenergic receptor of hypothalamic neurones which volley cold signals (Jell and Sweatman, 1977; Lin *et al.*, 1982).

The main reason why these authors have picked up NA as the mediator of PGE_1 or as the substitute for PGE_1 is that thermoregulatory responses elicited by PGE_1 and NA are similar and equally blocked by adrenoceptor antagonists and additionally, both of PGE_1 and NA activate the accumulation of cyclic-AMP (Exton, 1985) which could induce fever (Dascome and Milton, 1976)

Nevertheless the antagonism of adrenoceptor blocking agents in various effector mechanisms are not known in PGE_1-induced fever, since solely monitoring of rectal temperature was made in these experiments. Therefore we designed an additional study dealing with the interaction between PGE_1 and alpha-adrenoceptor blockade (tolazoline), in several effector responses.

MATERIALS AND METHODS

Male albino rabbits (n=28) weighing 2.2−2.5kg were locally anaesthetized and mid-section of skin were made. After the bur holes were made 1.5mm lateral from the Bregma, a 0.8mm ϕ polyethelene tubing was inserted until the regurging of cerebrospinal fluid was seen. Then tubing was attached to the cranial bone with araldite (Ciba-Geigy). These procedures were done under relatively aseptic condition.

Three to seventh day after the fixation of ventricular tubing, rabbits were unanaesthetized and fixed on the stereotaxic apparatus with monitoring the rectal temperature (Tre), the ear skin temperature (Tea) and respiratory frequency (RF). The ambient temperature was set at 26± 0.5°C. Commercially available prostaglandin E_1 (Prostandin, Ono), dissolved in saline at the concentration of 2 μg/ml, was microinjected into the lateral ventricle. The amount of injection was always 2 μl for each drug. Noradrenaline

(Sankyo) and tolazoline (Imidalin, Yamanouchi) were equally dissolved in saline at the concentration of 5 μg/ml.

The administration of these drugs was usually in bolus through the 30 gauge needle which was inserted immediately into the fixed tubing above the skull. Continuous infusion of tolazoline was made with the syringe pump (Terufusion STC-521, Terumo) at the rate of 10ng/min. Temperature monitorings were made by thermistor probes connected to the electrical thermometer (Shibaura Electronic Co.) and continuously traced on the paper recorder (Rikadenki). Respiratory frequency was measured by stringauge transducer tied around animal's trunk and counted by ATAC 450 computer (Nihonkoden).

1. PGE_1 vs tolazoline

Protocol (A): Pretreatment of tolazoline before PGE_1-administration was made by continuous perfusion. PGE_1 was administered during and after the perfusion.

Proocol (B): Tolazoline was administered 15 minutes after the injection of PGE_1. Thereafter, the injection of dipyron followed.

2. NA vs dipyron

Protocol (C): Dipyron was injected several times after the administration of NA.

Five series of experiments were performed on each protocol.

RESULTS

1. Prostaglandin E_1 vs Tolazoline

Tolazoline was both agonistic (Fig. 2, 3) and antagonistic (Fig. 1) to PGE_1-induced fever. The perfusion of tolazoline diminished the drop of Tea induced by PGE_1 in three cases out of protocol A experiments, while in other cases, it failed to affect on febrile responses. In Fig.1, the lowering of Tea was decreased during perfusion but after perfusion was stopped, the response restored and Tre rose. In all cases of protocol A, depressive effect of tolazoline on Tea was highly reproducible but it was not remarkable on RF change. The agonistic effects of post-injected tolazoline were observed either on Tea or RF (Fig.2). However, these effects were not remarkable when PGE_1 strongly evoked febrile responses (Fig.3). In four cases of protocol Bs, tolazoline didn't seem to affect on Tea and RF as shown in Fig.3. Only when PGE_1 failed to induce fever, tolazoline elicited fast drop of Tea and gradual decrease of RF (Fig.2). In one case (Fig.3), tolazoline elicited shivering among four cases in which PGE_1 succeeded to induce febrile responses.

Dipyron was additionally injected intraventricularly after the febrile responses were observed in the series of experiments of protocol B. Dipyron clearly increased RF in all the cases and also competed to the effect of lowering of Tea to considerable extent in four cases (Fig.2). Besides, shivering response induced by tolazoline was suppressed by dipyron.

On the whole, dipyron inhibited all the febrile responses which we have observed in the present experiments and post-injected tolazoline didn't antagonize the effects of PGE_1,

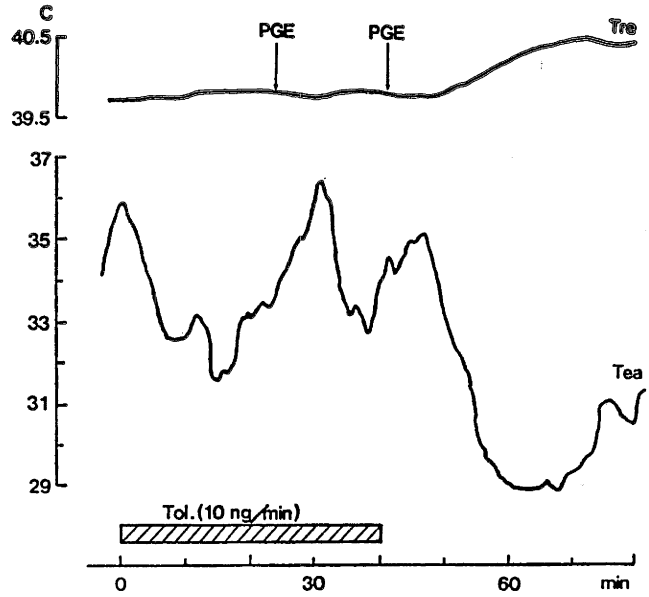

Fig. 1 The changes of rectal and ear skin temperatures in response to intraventricular injection of 4 ng of prostaglandin E_1 during and after the perfusion of tolazoline at the flow rate of 10 ng/min. Note the antagonistic effect of tolazoline as seen in ear skin temperature changes. Abbreviations, Tea; ear skin temperature, Tre; rectal temperature, PGE; prostaglandin E_1, Tol; tolazoline.

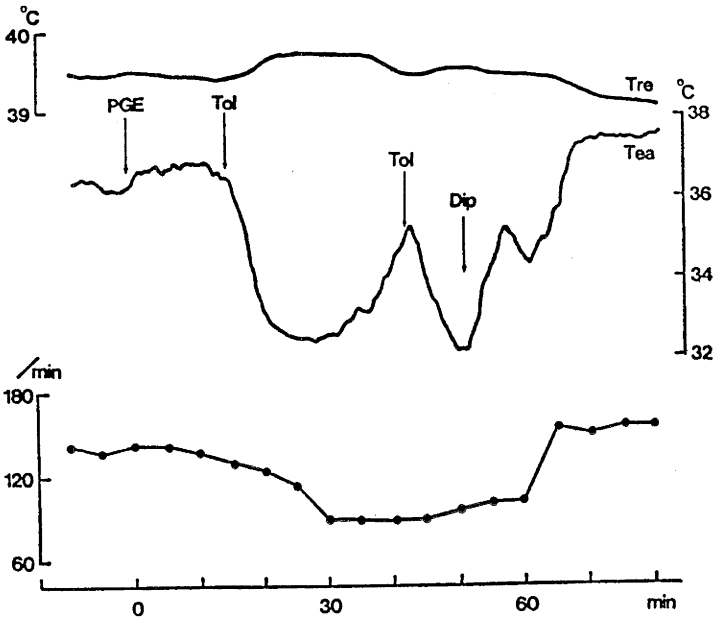

Fig. 2 Temperature and respiratory frequency changes under the series of successive administration of prostaglandin E_1, tolazoline and dipyron. Note weak but cooperative effect of tolazoline on both ear skin temperaure and respiratory frequency. And also note the competetive action of dipyron to tolazoline-induced febrile responses. Abbreviations, Dip; dipyron, others are same as in Fig. 1.

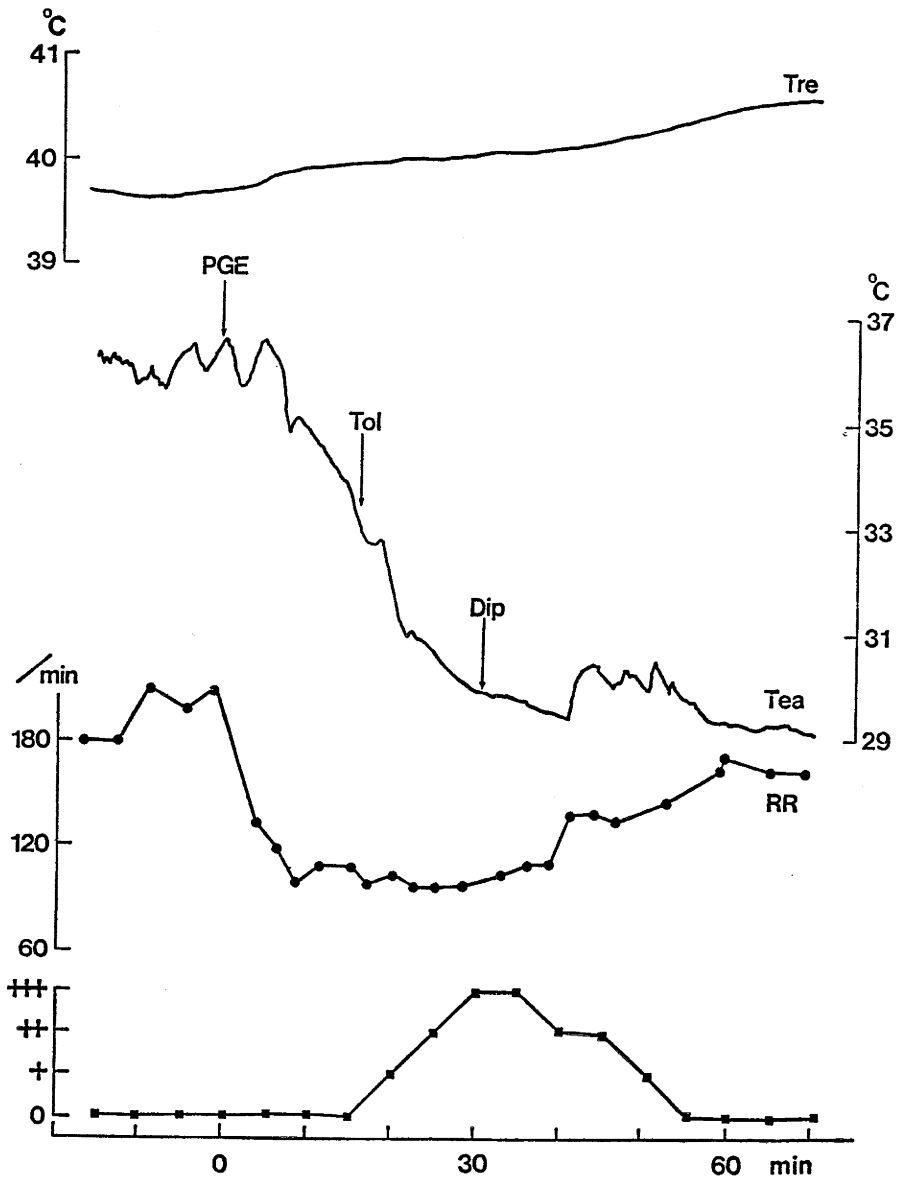

Fig. 3 The changes of temperatures and respiratory frequency are drawn with observed shivering. The intensity of shivering as indicated (+)~(卌) are, (+); local shivering of upper extremeties, (++); four extremeties shivering, (卌); general shivering. In this case prostaglandin E_1 induced febrile responses except shivering, however injection of tolazoline elicited shivering. Dipyron depressed shivering and competetively increased respiratory frequency but the effect on ear skin temperature was very weak and rectal temperature didn't fall enough. Abbreviations, SHIV; shivering, others are same as in Fig. 1.

rather it evoked additional febrile responses occasionally, and usually the effects of PGE_1 might hide the agonistic effects of tolazoline.

2. Noradrenaline vs Dipyron

In the previous report, the direct antagonism of dipyron against PGE_1 was observed in some effector activities such as Tea, RF and oxygen consumption (Iwamoto *et al.*, 1985). So in the present study, dipyron was injected after the administration of NA to investigate the participation of dipyron in adrenergic components in the volley of cold signals, since the present data have suggested this possibility. Differently to the effects of

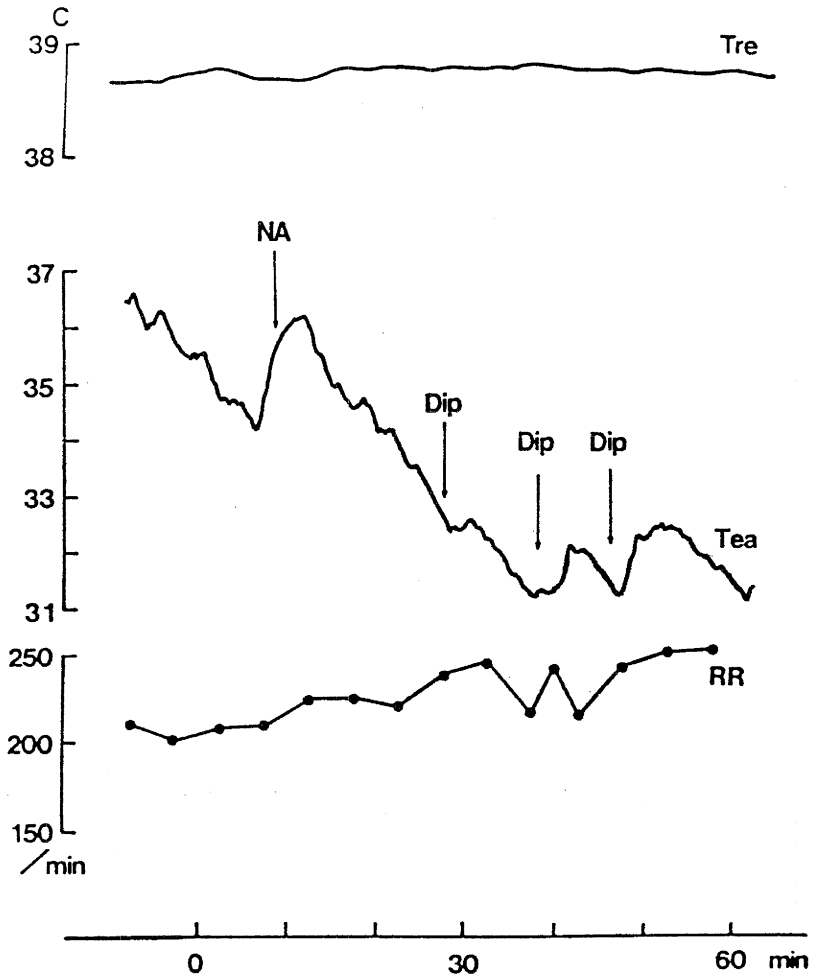

Fig. 4 Temperatures and respiratory rate change in response to successive administration of noradrenaline and dipyron. Noradrenaline of 10 ng couldn't raise rectal temperature, neither depressed the respiratory rate but ear skin temperature decrease was elicited. Dipyron slightly antagonized the effect of noradrenaline in ear temperature. Abbreviations, NA; noradrenaline, others are same as in Fig.1.

dipyron on PGE_2-induced fever, the results have shown the antagonism of dipyron only in Tea in all the cases, since RF was rarely decreased by NA. The control study of dipyron showed no effect in effector activities, however, the control studies of tolazoline have revealed its direct action on Tea. Large dose of tolazoline lowered Tea (Fig.5). Not making enough number of experiments, however it would seem that tolazoline lowered Tea in dose-dependent manner and the higher the Tea, the greater the effect.

Summarising these complicated data from the stand point of effector mechanisms,

1. Tea was aways lowered by PGE_1 and NA and relatively large dose of tolazoline.
2. Lowering of Tea induced by PGE_1 was inhibited by pre-treatment of tolazoline.
3. Lowering of Tea induced by PGE_1 was *not* inhibited by post-injected tolazoline
4. RF was decreased by PGE_1 or tolazoline *not* by NA
5. The decreased of RF induced by PGE_1 was always antagonized by dipyron
6. Shivering was induced by tolazoline *not* by NA
7. Shivering was diminished by dipyron

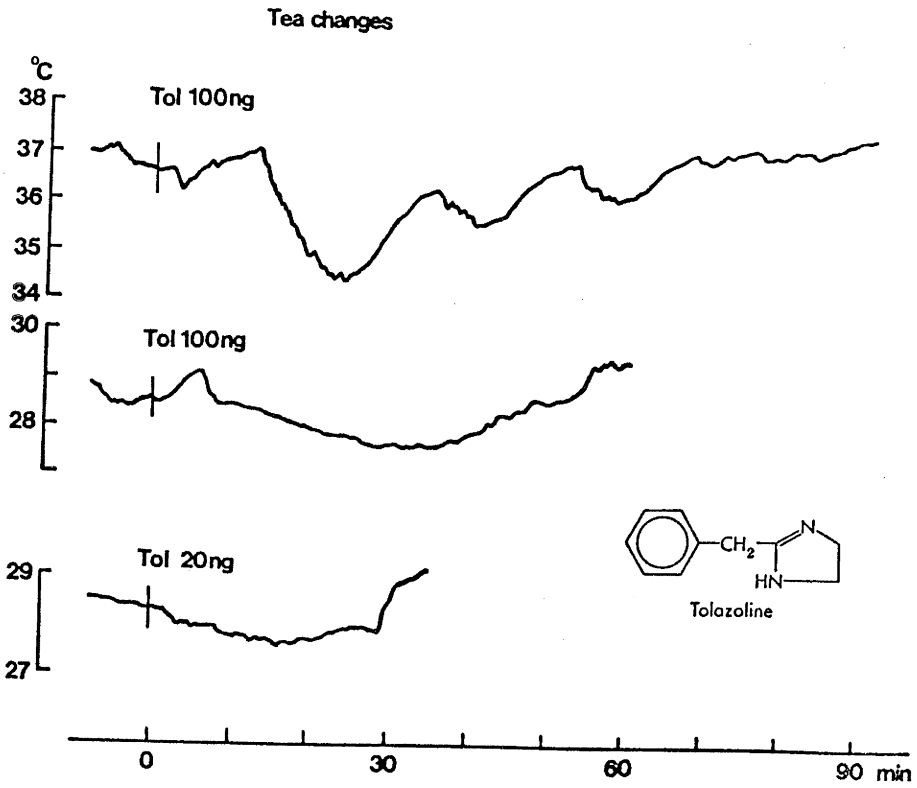

Fig.5 The changes of ear temperature in response to large-dose of tolazoline. Weak lowering effect is seen dose-dependently. This effect is similar to that of noradrenaline or prostaglandin E_1. And the effect is more remakable at higher ear skin temperature.

DISCUSSION

Fever is, of course, different from hyperthermia. As a symptom, fever is characterised by various effector activities; sometimes the chilness of hands and feet is only the symptom, or in a severe case, strong shivering accompanies with rigidity of extremities. Therefore, the rise of rectal temperature is merely the general reflection of specific effector activities. For example, warming of spinal cord easily diminished shivering induced by the administration of LPS of *E. coli* in rabbits (Iwamoto *et al.*, 1985), however in such case, Tre kept rising, on the other hand RF and Tea didn't rise. So we dare say it is important to estimate each effector activity when the study of the antagonism of adrenergic blockades on PGE_1-fever.

Both PGEs and NA can induce hyperthermia in rabbits but NA depressed shivering at low ambient temperature (Feldberg and Myers, 1964; Feldberg and Saxena, 1971), while PGEs usualy evoke consonant febrile responses. Alpha-adrenoceptor blocking agents blocked hyperthermic responses induced by NA (Dhawan and Dua, 1971) or PGE_1 (Laburn *et al.*, 1975), and it solely induced hypothermia in the rabbit (Feldberg and Saxena, 1971). Nevertheless, it is not known what effector was activated or inactivated. So the antagonism of each effector responses will be discussed.

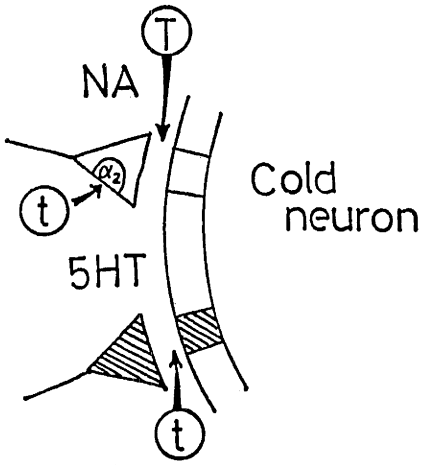

Fig.6 Possible action sites (arrows) for tolazoline on synaptic components of cold responsive neuron of which pharmacological characteristics are based on the results of single unit study made by Hori and Nakayama. Synaptic inputs are schematically represented by blank (NA) and hatched triangles, which are facilitatory and inhibitory inputs, respectively. Antipyretic effect of tolazoline is drawn as capital "T". Here tolazoline blocks the facilitatory inputs transmitted by noradrenaline. This manner was already proposed by Lin *et al.* Small letters "t" are febrile action sites for tolazoline which would depress the inhibitory inputs from serotonergic nerve ending or inhibit the alpha 2-adrenoceptor presynaptically. In the case that, adrenoceptors would be fully occupied PGE_1, tolazoline may act on other receptor sites as indicated by "t" s.

1. *Action of PGE_1 and Tolazoline*

In present data, tolazoline-pretreated animals couldn't develop febrile responses to intracerebroventricular injection of PGE_1 which is consistent with other authors' reports (Dhawan and Dua, 1971; Feldberg and Saxena, 1971). On the contrary, PGE_1-pretreated animals, febrile or afebrile, showed the potentiated response in the drop of Tea by tolazoline, whereas other effector responses were not affected. One reason for accounting this discordance may be due to relatively wide-range administration of PGE_1 into ventricular space. However, the concentration of intraventricular PGE_2 during intravenous administration of leukocyte pyrogen is a few nanogram per mililiter (Coceani *et al.*, 1983). The origin and secretory system of PGEs are also obscure. In addition, there is no evidence that PGEs would act only at extremely narrow site, or that PGEs might be para-secreted to elicit wide-range responses. So it is difficult to mention that cerebroventricular dosage of PGEs are disadvantageous.

Tolazoline is not salective but both alpha 1-and alpha 2-adrenoceptor antagonist (Exton, 1985). And as in Fig.5, tolazoline in large dose has weak vasoconstriction effect on rabbit ear when it is injected into ventricular space. These agonistic and antagonistic effects might have resulted from the different action sites in synaptic components, since tolazoline is also the antagonist of 5-HT. It is note worthy that, tolazoline in large dose ex-

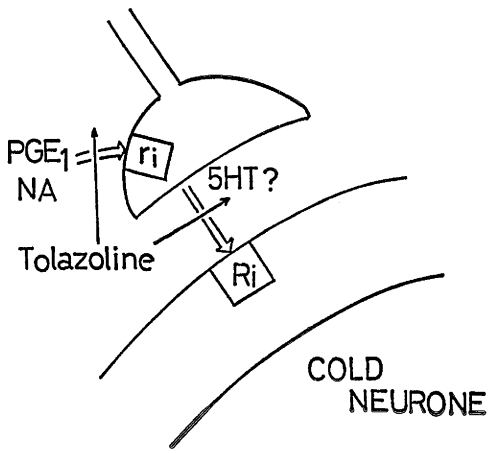

Fig.7 A simple model of synaptic connection between warm and cold responsive neuron based on findings of Kelso and Boulant. There is no evidence that the transmitter should by be 5-HT, so it might be NA as well. The dogma which we have applied is that PGE_1 would diminish the release of transmitters by lowering Ca^{2+} ion influx as proposed by Mo. Therefore, whatever the transmitter is, it should activate postsynaptic *inhibitory* receptors as indicated by "Ri". Presumably presynaptic inhibitory receptor (ri) would be alpha 2-adrenoceptor. Low-dose of extrinsically applied tolazoline might be the antagonist for "ri", the action of PGE_1 and NA depressed. High-dose of tolazoline would act on postsynaptic receptor to depress the inhibitory inputs which are responsible for febrile responses.

pressed cold defense mechanism because, in singie-units study, Hori *et al.*, have reported cold responsive neurones increase firing rate by the application of NA but depressed by 5-HT (Hori and Nakayama, 1973). Therefore it is assumed that large-dose tolazolin or postinjected tolazoline might act on the postsynaptic 5-HT receptor which receives inhibitory serotonergic synaptic inputs or on the presynaptic alpha 2-adrenoceptor which acts on the facilitatory nerve ending to cold responsive neuron. In Fig.6, schematic drawing provides possible action sites for tolazoline.

According to Mo *et al.* (1985), PGE_1 depresses calcium conductance of membrane of rabbit superior cervical ganglion neurones and this procedure eventually would occur at the nerve terminals to inhibit the release of transmitter by the interferense of Ca^{2+} influx. The modulation of prostaglandins has been proposed by many investigators and presynaptic inhibition would be predicted as one of the action modes (Belluzi *et al.*, 1983; Brody and Kadowitz, 1974; Hedgvist, 1974). These findings endow us the close resemblance to the inhibitory action of alpha 2-adrenoceptor reported by Horn and McAfee (Horn and McAfee, 1980).

Thus, complicated problems newly arise here. If cold responsive neurones would have adrenergic facilitatory synaptic inputs as previously assumed, how PGE_1 could evoke the stimulation of cold neurones by its presynaptic inhibition ? Or does PGE_1 act on postsynaptic adrenoceptor of cold responsive neuron to increase is firing rate through the depression of Ca^{2+} influx which is requisite for adenylate cyclase activity (Daly *et al.*, 1977) ?

On the other hand, resulting from single-units studies in preoptic and anterior hypothalamic area of rabbits, Stitt have predicted that PGE_1 would modulate the release of NA presynapcically, since warm or cold neurones are equally facilitated by PGE_1 and NA doesn't antagonize the effect of PGE_1 (Still and Hardy, 1975). Jell *et al.* have reported PGE would act on common sites of NA and 5-HT where peripheral thermal inputs terminate (Jell, 1974; Jell and Sweatman, 1977). However these findings are not sufficient to provide content information upon synaptic events occurring in hypothalamic thermoregulatory center.

According to Kelso *et al.* (Kelso *et al.*, 1982; Kelso and Boulant 1982) cold neurones are merely interneurones which receive inhibitory synaptic inputs from warm responsive (or warm receptor) neurones. This evidence would enable us to conclude that PGE_1 might stimulate the alpha 2-adrenoceptor of the nerve terminals of warm neurones which are the inhibitory inputs to cold responsive neurones then depression of transmitter release is elicited by PGE_1, and cold responsive neurones increase their firing rates. Tolazoline, applied extrinsically in low dosage, would antagonize the binding of NA and PGE_1 to this alpha2-adrenoceptor and large dose of tolazoline might depress the postsynaptic inhibitory receptor, by which cold defense mechanisms are evoked. Nevertheless it is not clear whether this postsynaptic receptor would be serotonergic or adrenergic.

In rats (Murakami, 1973) and rabbits (Hori and Nakayama, 1973), cold responsive neurones are depressed by 5-HT and facilitated by NA. In addition, considering some

evidences that presynaptic alpha 2-adrenoceptor modulates serotonergic nerve terminals in hypothalamus (Galzin *et al.*, 1984) and cortex (Gothert an Huth, 1980) in rats, conceivable hypothesis would be as drawn in Fig. 7.

2. *Action of Dipyron*

Usually, the efficacy of antipyretics such as salicylates and indomethacin is explained by their inhibitory effects on prostaglandin synthetase (cyclo-oxygenase) (Flower, 1974). However, as previously reported, dipyron has direct effects on PGE_2-induced fever in rabbits (Iwamoto, 1985). The competetive response of dipyron against PGE_2 have been observed not only in rectal temperature but also respiratory frequency, ear skin temperature and oxygen consumption. One of tentative answers was that dipyron might act on presynaptic morphine receptors (Ivanov and Staneva-Stoycheva, 1984), since morphine is the effective antagonist of PGE-activated brain adenylate cyclase (Daly, 1977). In present data, dipyron has depressed tolazoline-induced shivering and NA-induced drop of Tea. So dipyron may have roles in adrenergic components. However, further study is required for revealing the action site of dipyron.

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プロスタグランディン E_1 発熱におけるトラゾリンの効果に関する研究

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無麻酔下の雄の家兎について，側脳室留置カテーテルにより種々の薬剤を投与し，発熱及び解熱過程における効果器活動を測定した．プロスタグラディン E_1 (PGE_1) によって惹起された耳介皮膚温（Tea）の低下と呼吸数（RF）の低下は，前投与された α ブロッカーであるトラゾリン（Tol）によって抑制されたが，後投与された Tol からは抑制をうけず，むしろ PGE_1 による効果器活動を促進した．スルピリン（Dip）はこれらの反応を抑制した．また，ノルアドレナリン（NA）は Tea の低下を惹起したが，RF に対しては著明な反応を示さなかった．この NA による Tea の低下に対して，Dip は抑制的に働き Tea の上昇を促した．非選択的 α ブロッカ

ーであり，5HT のブロッカーでもある Tol は，単独投与でも Tea の低下を惹起した．Tol の相反する2種類の作用は，それが抑制するレセプターの相違によって生じるものと思われるが，文献的考察も加えると，PGE_1 と前投与した Tol の作用部位はおそらく前シナプス性の α_2-レセプターではないかと推察される．又，後投与した Tol の作用部位は冷信号伝搬に関係した細胞の後シナプス性のレセプター（抑制性）ではないかと思われる．

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