the brain, reducing the half-time from a mean of 193 min to 95 min, 48% of the control value ($p < 0.05$). 6-OHDA had a comparable effect, reducing the half-time to 80 min, 42% of control ($p < 0.025$). 30 days after 6-OHDA treatment the diffusion half-time had returned to control values. The mean diffusion half-time after pimozide pretreatment was 197 min, not significantly different from controls. The intercepts and half-times of the fast component did not appear to be significantly altered by any of the pretreatment drugs. Representative scintiphotos in figure 2 show that the ^{68}Ga was initially in the brain, then appeared transiently in the kidneys and then began to concentrate in the bladder; it was not seen in any other organs.

Discussion. The results obtained here are quite similar to those found for diffusion of ^{24}Na from blood into CSF by Levin and Patlak[11]. These authors found a rapid component with a $T_{1/2}$ of about 5 min and intercept of 0.56, and a 2nd, slower component of $T_{1/2}$ about 2 h; with some reservations, they attributed these to blood-CSF exchange and brain extra-cellular space (ECS) - CSF exchange, respectively. The fact that the intercept for the fast component found here was smaller, 0.11, probably reflects the fact that the label was placed in the CSF rather than in the blood, allowing a proportionately greater fraction to enter the ECS of the brain.

It is difficult to compare the results of the many different methods of measuring brain diffusion parameters, and we have not developed a mathematical model of analysis of our data. All authors seem to agree, however, that diffusion half-times are valid indicators of the status of the BBB with respect to the molecule being used as an indicator. The relative simplicity of our method compared to other techniques allows comparison of the effects of various drugs on the brain diffusion of a non-electrolyte which labels the ECS. It allows comparison of the effects of drugs in the same animal, an important consideration when the control values are as variable among animals as found here, yet they are consistent on repeat tests in the same animal.

In these initial studies we have investigated the effects of 2 drugs which have been linked to schizophrenia. Both amphetamine and 6-OHDA increased the diffusion of ^{68}Ga-EDTA out of the brain, reducing the $T_{1/2}$ by a factor of 2. Pimozide, which is believed to exert its anti-psychotic action by blocking the post-synaptic DA receptors, had no effect. It seems too simplistic to suggest that amphetamine, in addition to its known effects, induces psychotic symptoms by simply lowering the brain's barrier to toxins, or specifically to dopa which would be immediately converted to dopamine thus producing a hyperdopaminergic state. Although there is little or no evidence that 6-OHDA occurs in brain, it has the same effect on the BBB in our experiments as amphetamine. Although 6-OHDA is known to produce irreversible damage to nonadrenergic and dopaminergic tracts in the CNS, the effect on the BBB had disappeared by 30 days. It can only be assumed in these studies that passive diffusion as measured with ^{68}Ga-EDTA is the same in both directions across the BBB.

The method described here is potentially applicable to any compounds which can be labelled with a gamma-emitting radioisotope of energy suitable for use with a scintillation camera, i.e., with gamma energies less than $\simeq 400$ keV, or which emits positrons. Ideally, the compound should also not be appreciably metabolized and be selectively removed by the kidney. The method should be applicable to the study of a variety of other compounds which could be appropriately labelled, and the effects of various drugs on their diffusion out of the brain.

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Antidiuretic and thermogenic effects of intracerebroventricular prostaglandin H_2 in ethanol-anaesthetized rats

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Summary. When PGH_2 was administered intracerebroventricularly at doses of 5 and 15 nmoles in ethanol-anaesthetized rats, alcohol diuresis was inhibited and rectal temperature, blood pressure and heart rate were all significantly increased.

It is well known that prostaglandins (PGs) of the E series applied into the cerebroventricle inhibited water diuresis[1] and increased plasma and urinary concentrations of antidiuretic hormone (ADH)[2,3]. The present authors demonstrated that PGE_2, when administered into the lateral ventricle in ethanol-anaesthetized rats caused diuresis followed by antidiuresis[4,5]. Centrally injected $PGF_{2\alpha}$ and PGA_2 also changed urine outflow in the rat[4,6,7]. These findings led to the concept that PGs in the central nervous system played important roles in water metabolism.

On the other hand, the endoperoxide intermediates PGH_2 and PGG_2, identified in the PG biosynthetic pathway[8–10], were found to have some biological activities in the peripheral tissues[11–13]. Hitherto, there have been few reports concerning the effects of PGH_2 or its analogues on the central nervous system. In this study, therefore, we have investigated the effects of intracerebroventricularly (i.c.v.) administered PGH_2 on urine outflow in ethanol-anaesthetized rats. Since it has already been reported that central PGE[14–17]and PGH_2 analogues[18] changed body temperature,

it was also decided to investigate the effect of i.c.v. injected PGH_2 on body temperature.

Methods and materials. The methods used have been described elsewhere in detail[19]. In brief, male Wistar rats (280–300 g), starved for about 18 h, were anaesthetized with oral administration of 12% ethanol in a volume of 50 ml/kg. Anaesthesia was maintained with i.v. infusion of 3% ethanol at a rate of 0.1 ml/min. Steel cannulae were inserted into the lateral ventricle and the cerebral aqueduct. An artificial cerebrospinal fluid (CSF) was perfused from the lateral ventricle to the cerebral aqueduct at a rate of 10 µl/min. The ionic composition of the CSF was as follows (mEq/l): Na^+; 150, K^+: 3, Ca^{++}; 2.3, Mg^{++}; 1.6, Cl^-; 135, HCO_3^-; 21, HPO_4^{--}; 0.5. Urine was collected through a bladder cannula and the rate of urine outflow was recorded by a photoelectric drop counter. Results were expressed as a percentage of change by PGH_2 in urine outflow, and pre-PGH_2 levels (expressed as 100%) of urine outflow were in the range from 0.9 ml/10 min to 1.3 ml/10 min. Body temperature (B.T.) was recorded through a thermistor probe inserted about 5–6 cm into the rectum. Blood pressure (B.P.) and heart rate (H.R.) were measured through a cannula inserted into the carotid artery and by an electrocardiograph, respectively. PGH_2, kindly supplied by the Ono Pharmaceutical Co., Ltd, Osaka, Japan, was dissolved in the CSF to give concentrations of 1, 5 and 15 nmoles/10 µl immediately before use, since PGH_2 was extremely labile. PGH_2 in the CSF was slowly (10 µl/min) administered through the lateral ventricular cannula at a volume of 10 µl. In some experiments, antidiuretic hormone (Pitressin, Parke-Davis, USA) was injected i.v. at doses ranging from 25 to 200 µunits/animal.

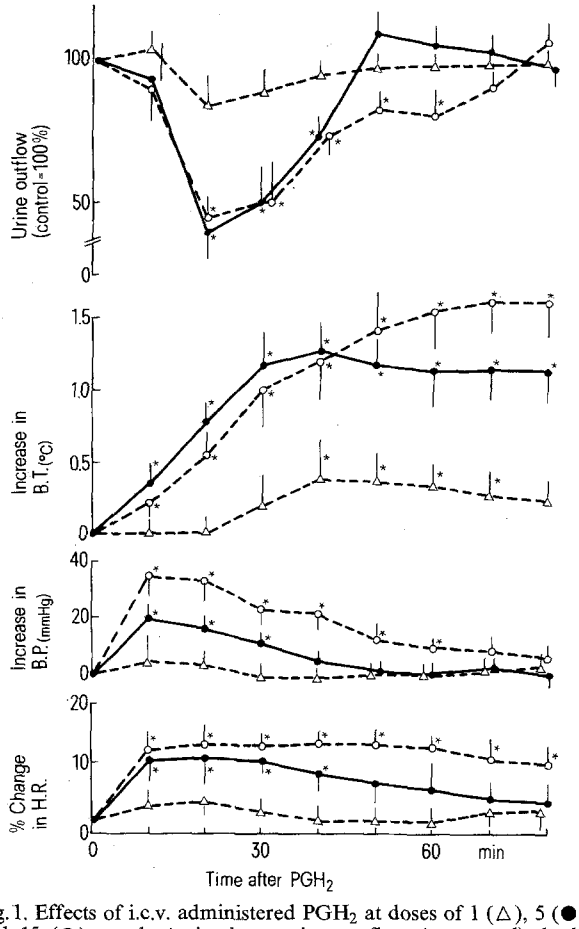

Fig. 1. Effects of i.c.v. administered PGH_2 at doses of 1 (△), 5 (●) and 15 (○) nmoles/animal on urine outflow (top panel), body temperature (B.T.), blood pressure (B.P.) and heart rate (H.R., bottom panel). Pre-PGH_2 values of urine outflow, B.T., B.P. and H.R. were 6.8±0.5 ml/h, 37.2±0.8 °C, 108±4 mm Hg and 440±16 beats/min, respectively. Abscissa: time (min) after the i.c.v. administration of PGH_2. Bars represented SEM in 8–12 instances. *Significant difference from pre-PGH_2 values ($p < 0.05$).

Results. PGH_2, when administered into the lateral ventricle at a dose of 5 nmoles, decreased urine outflow and increased B.T., B.P. and H.R. (figure 1). In addition, increasing the dose of i.c.v. PGH_2 to 15 nmoles did not produce a significant additional decrease in urine outflow and increase in B.T., B.P. and H.R. However, the antidiuretic and the hypertensive responses produced by PGH_2 at 5 nmoles were short-lived (30–40 min) and these responses produced by 15 nmoles were relatively long-lasting (60 min). Tachycardia in response to PGH_2 (5 nmoles) lasted for 40 min but the effect of 15 nmoles PGH_2 on H.R. lasted for more than 80 min. On the other hand, during the observation period of 80 min, there was no significant difference between time-response curves for the thermogenic effects of PGH_2 at the doses of 5 and 15 nmoles. PGH_2 at the dose of 1 nmole did not change urine outflow, B.P. and H.R., but did increase B.T. This effect became significant 40 min after the i.c.v. administration and lasted for 40 min. When antidiuretic hormone (ADH) was injected i.v. at doses ranging from 25 to 200 µunits/animal, alcohol diuresis was inhibited in a dose-dependent manner (figure 2), but B.T., B.P. and H.R. remained unchanged.

Discussion. There is evidence to suggest that PGE can act centrally to stimulate the ADH release. The infusion of PGE_1 into the 3rd ventricle[1] and the lateral ventricle[3] inhibited water diuresis, caused the release of ADH and increased renal Na^+ excretion in conscious, hydrated goats. In addition, the ventriculo-cisternal perfusion with PGE_2 resulted in an increase in plasma ADH concentration in urethane-chloralose-anaesthetized dog[2]. On the other hand, we have previously observed that PGE_2, when perfused from the lateral ventricle to the aqueductus cerebri in the ethanol-anaesthetized rat, caused diuresis followed by antidiuresis[4,5]. In this study, therefore, we infused 3% ethanol i.v. for maintenance of anaesthesia and diuresis, and then compared effects of i.c.v. administered PGH_2 and PGE_2. Unlike PGE_2, PGH_2 did not cause diuresis, but inhibited alcohol diuresis. Although it is well known that ethanol inhibits the ADH secretion and causes diuresis, i.e. alcohol diuresis, it has been suggested that the effect of ethanol was

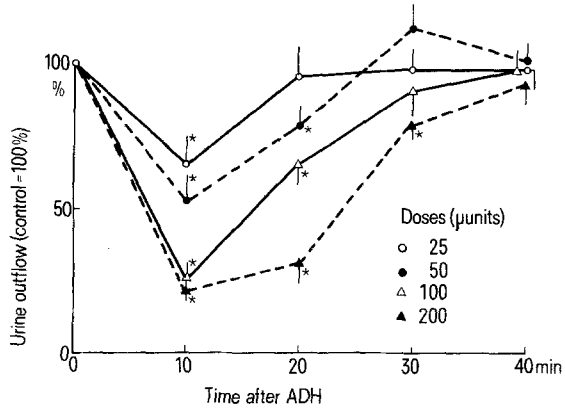

Fig. 2. Effect of ADH at i.v. doses of 25 (○), 50 (●), 100 (△) and 200 (▲) µunits/animal on urine outflow. Ordinate: urine outflow (pre-ADH level, 0.9–1.3 ml/10 min as 100%), abscissa: time (min) after the i.v. injection of ADH. Bars indicate SEM in 8–12 instances. * Significant difference from pre-ADH levels ($p < 0.05$).

restricted to ADH release caused by osmotic stimuli[20]. Therefore, the possibility should not be excluded that central PGH_2 stimulated the ADH secretion.

It is assumed that hypertension and tachycardia induced by central PGH_2 is not due to evoked release of ADH, since antidiuresis in response to PGH_2 (5 nmoles) was roughly similar to that produced by ADH at i.v. doses of 100–200 μunits/animal, which did not change B.P. and H.R. In fact, a few milliunits/animal of ADH was required to elevate B.P. by 10–30 mm Hg in the ethanol-anaesthetized rat. In addition, this hypertension was associated with bradycardia (data not shown).

Cremades-Campos and Milton[18] reported that some stable analogues of PGH_2 increased B.T. but its isomer decreased it in conscious cats. We also observed that i.c.v. injected PGH_2 increased B.T. by 1.3–1.5 °C in the ethanol-anaesthetized rat. Unlike the antidiuretic effect, the thermogenic effect of 5–15 nmoles PGH_2 reached a maximum at 40–60 min, suggesting that both effects were independent of each other. In fact, PGH_2 at the dose of 1 nmole by which urine outflow, B.P. and H.R. were not varied significantly, produced the rise in rectal temperature.

Since PGH_2 injected i.v. at the dose of 15 nmoles/0.1 ml was without effect, it was unlikely that i.c.v. administered PGH_2 was transferred to the systemic circulation to reveal the effects observed by the central administration of PGH_2. The effects of i.c.v. PGH_2 were rather central in origin.

Further experiments are under way to elucidate the mechanisms for the antidiuretic and the thermogenic effects of i.c.v. PHG_2.

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Evidence for an aphrodisiac pheromone of female *Drosophila*

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Summary. We report here direct evidence for the involvement of a pheromone in the induction of male wing vibration, an important fixed action of the *Drosophila melanogaster* courtship pattern. This chemical stimulus is produced by mature females but not by mature males. The behavioral response is proportional to the pheromone concentration.

Chemical communication is a favoured way of communicating among insect individuals, especially for sexual communication which climaxes in the copulatory act[2,3]. One or both sexes produce pheromones which induce specific behavioral responses of the mate. According to their distance of action, pheromones can be classified as attracting and/or aphrodisiac substances. As far as their emission is concerned, pheromones are synthesized in specialized endocrine cells, very often under a neuro-endocrine control, and then are transported towards the exterior by specialized ducts. In some cases, pheromones may diffuse out towards the other individuals and in other cases, pheromones are sensed by direct contact between individuals. As far as their detection is concerned, specialized receptors are involved, which are able to transform the chemical signal into an electrical signal which is transferred via the sensory neurons towards a decoding central structure. More and more examples now provide evidence for not only 1 sex specific chemical but for several chemicals with active roles as well as regulatory roles (synergy, inhibition). For example in the Dipteron *Musca domestica*, a female specific attracting substance, cis-9-tricosene, was isolated in 1971 by Carlson et al.[4]. More recent studies have shown the male attracting power of a large number of cis-9 alkenes containing 19–25 carbons and the aphrodisiac role of other cuticular lipids including cis-14-tricosen-10-one and cis-9, 10 epoxytricosane[5,6].

Our deep understanding of the genetic technology of *Drosophila melanogaster* offers a valuable tool for the dissection of such a chemical communication system[7]. Once a male has sensed the presence of a female, he displays a set of fixed action patterns which have been described in great detail[8,9]. The nature of the female stimuli has also led to numerous and diverse studies whose results are not easy to interpret. As early as 1915, Sturtevant[10] observed that a hetero-pair of flies (consisting of a male and a female) mated more rapidly in vials which had previously held copulating pairs than in clean ones, a result which could not be confirmed by Ewing and Manning[11]. Shorey and Bartell observed that in a Y type olfactometer, males were attracted into the branch where a female odour had been blown and then tended to orient towards each other[12]. The involvement of female chemical stimuli has also been strongly suggested by studies of population genetics[13].

Wing vibration is the most conspicuous among the male's early courtship signals. We have chosen to concentrate on it and to define female sex appeal as the stimulus (or set of stimuli) which induces it in male courters[14]. We have recently reported the ontogenies of both the emission of sex appeal and its detection leading to the vibration response.