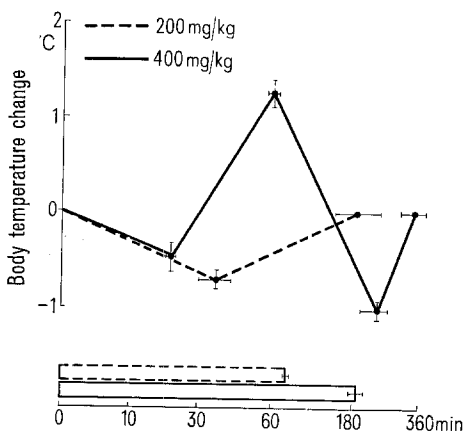
γ-Butyrolactone: An Anesthetic with Hyperthermic Action in the Rat

γ-butyrolactone (GBL) is an anesthetic agent with some interesting properties: It causes a selective increase of brain dopamine presumably by antagonizing transmitter release from nerve terminals, as has been shown with biochemical[1,2] and fluorescence microscopic methods[3]. Moreover, GBL has been reported to be an endogenous brain metabolite derived from glutamate through γ-aminobutyrate[4]. We now report a hyperthermic action of GBL in the rat which is a unique feature for an anesthetic compound.

Experiments were performed in unrestrained, male albino rats held in individual cages at an ambient temperature of 30 °C. Body temperature was continuously monitored with an intraperitoneal temperature transmitter[5,6] which had been implanted approximately 1 week before the experiments. Motor activity was measured with a force recorder[5] placed under the animal's cage. GBL was administered by intraperitoneal injection at doses of 200, 400, and 700–800 mg/kg, using a counterbalanced design with intervals of at least 2 days between experiments.

A dose of 200 mg/kg GBL abolished spontaneous motor activity for 87 min and decreased body temperature by 0.7 °C (± 0.09 SEM) (Figure). A dose of 400 mg/kg abolished motor activity for approximately 3 h. Immediately after administration of the drug body temperature decreased by 0.5 °C (± 0.13 SEM). Approximately 20 min after injection, body temperature started to rise, and reached a peak of 1.3 °C (± 0.16 SEM) above the control level after 70–90 min. Subsequently, body temperature decreased to 1 °C (± 0.11 SEM) below the initial level, at a time when the animal started to resume spontaneous motor activity. Doses of 700–800 mg/kg GBL which depressed motor activity for 5–8 h, had a similar triphasic action on body temperature with a peak of 1.5 °C (± 0.37 SEM) above the control level. However, with such high doses a prolonged depression of motor activity, feeding and drinking was apparent in some animals, indicating a possible toxic effect. To test the possibility that the changes of body temperature are due to an increase of cerebral dopamine, synthesis of catecholamines was inhibited with α-methyl-*p*-tyrosine methyl ester (AMPT; 250 mg/kg i.p. 40–70 min prior to GBL). It had been shown previously[1] that the increase of brain dopamine by γ-hydroxy butyrate (GHB; a metabolite of GBL) could be prevented by pretreatment with AMPT. In our experiments pretreatment with AMPT did not significantly influence the effect of GBL (400 mg/kg) on body temperature (peak increase 1.0 °C ± 0.22 SEM) and motor activity. Therefore, it seems unlikely that these effects are due to an increase of brain dopamine. The high level of endogenous GHB in the hippocampus and mesodiencephalon of the guinea-pig[2] raise the possibility that exogenous GBL might exert some of its effects by acting on non-dopaminergic cerebral structures. Recent experiments in chronic thalamic rats[7] indicate that the presence of telencephalic structures is necessary for GBL hyperthermia, as the rise of body temperature was practically abolished in this preparation, whereas hypothermia and anesthesia were still present. It remains unknown, however, by what mechanisms GBL induces hyperthermia during anesthesia.



Effect of γ-butyrolactone (--- 200 mg/kg and — 400 mg/kg) on body temperature. The means and standard errors of the minimum and maximum values, and the time of return to the baseline level are shown for 5 subjects. The horizontal bars represent the duration of abolished motor activity for the 2 doses.

Zusammenfassung. γ-butyrolacton (400 mg/kg i.p.) bewirkt bei der Ratte eine triphasische Änderung der Körpertemperatur mit einer hyperthermen Komponente. Diese für ein Narkosemittel ungewöhnliche Hyperthermie kann nicht durch eine Erhöhung der Dopaminkonzentration im Gehirn erklärt werden, da sie nach Hemmung der Katecholaminsynthese immer noch vorhanden ist.

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[1] G. L. Gessa, F. Crabai, L. Vargiu and P. F. Spano, J. Neurochem. *15*, 377 (1968).
[2] R. H. Roth, Biochem. Pharmac. *19*, 3013 (1970).
[3] G. K. Aghajanian and R. H. Roth, J. Pharmac. exp. Ther. *175*, 131 (1970).
[4] R. H. Roth and N. J. Giarman, Biochem. Pharmac. *19*, 1087 (1970).
[5] A. A. Borbély, in Proc. 4th Int. Congr. of Pharmacology, Basel 1969 (Schwabe, Basel/Stuttgart 1970), vol. V, p. 295.
[6] H. Graf and A. Borbély, Experientia *22*, 339 (1966).
[7] A. A. Borbély, J. P. Huston and I. R. Baumann, in *The Pharmacology of Thermoregulation* (Eds. P. Lomax and E. Schönbaum; Karger, Basel), in press.
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Transfer of Metallic Mercury into the Foetus

Metallic mercury is known to cross the blood brain barrier much more readily than ionic mercury[1,2]. No similar studies have been reported on the relative transport rates of these forms of mercury from mother to foetus.

In the present study Wistar rats 200–300 g were exposed to mercury vapour labelled with the ^{203}Hg isotope to give a specific activity of 15 μCi/μg of mercury. The animals placed in metabolic cages were allowed to inhale

Transfer of elemental and ionic mercury from mother to foetus

Group	Form of Hg	Body burden (μg Hg)	No. of mothers	Total Hg in maternal blood (ng)	Mercury in Placental-foetal units No. of units	Total Hg (ng)	Placental-foetal mercury in foetus (%)
A	Hg	1.9	4	28 ± 3.5	36	9.0 ± 0.4	47
B	Hg^{++}	1.9	4	730 ± 10.3	37	10.6 ± 0.6	1.0

the radioactive mercury vapour for $2^1/_2$ min and then sacrificed by decapitation (group A). The body burden of inhaled vapour was determined by whole body counting. Another group of animals (group B) was given labelled mercuric chloride by i.v. injection in a dose equivalent with the body burden of rats belonging to group A. They were killed $2^1/_2$ min after injection. Radioactivity was measured in the combined placental-foetal unit and in the separated foetuses and in 1 ml samples of maternal blood.

Data in Table demonstrate that the amount of mercury in blood was over 25 times greater in animals injected with ionic mercury than in vapour exposed rats. This difference is probably due to the fact that metallic mercury rapidly diffuses from blood to tissues as reported previously. Despite this difference in blood levels the total amount of mercury taken up by the placental-foetal unit was approximately the same. However, in animals exposed to the radioactive vapour nearly half of the mercury taken up by the placental-foetal unit was found in the foetus compared with 1% in the group injected with inorganic Hg.

These results indicate a potential for damage to the foetus in situations of exposure to mercury vapour. Exposure of women to mercury vapour occurs in certain occupations such as in the preparation of thermometers and calibration of pipettes[3]. Our results therefore suggest a need for teratological studies in relation to exposure to mercury vapour.

Zusammenfassung. Der Quecksilbergehalt im Mutterblut von Ratten war nach Injektionen von Quecksilbersalz 25 mal höher als derjenige von mit radioaktivem Quecksilberdampf behandelten Muttertieren. Auf den Foetus ging hingegen 47 mal mehr Quecksilber über, wenn das Muttertier Quecksilberdämpfen ausgesetzt wurde.

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1 M. BERLIN, L. G. JERKSELL and H. UBISCH, Archs envir. Hlth. *12*, 33 (1966).
2 L. MAGOS, Br. J. indust. Med. *25*, 315 (1968).
3 D. GOLDBLATT, M. R. GREENWOOD and T. W. CLARKSON, Neurology *21*, 433 (1971).

Metabolic Requirements for the Uptake and Retention of H^3Norepinephrine (H^3NE) by Isolated Frog Ventricle

The incorporation of NE into granules in the nerve terminals in situ is an active process requiring energy[1,2]. In isolated left atrium of the guinea-pig, the energy utilized for NE uptake in the nerve endings can procede from glycolysis of exogenous glucose or oxidation of non-carbohydrate endogenous substrates[3]. However, in isolated frog ventricle under anoxia, exogenous glucose cannot serve as an adequate source of this energy[4]. In the present paper the metabolic requirements for the uptake and retention of H^3NE by isolated frog ventricle are studied.

Methods. Ventricles of frog (*Rana pipiens*) were prepared and mounted as previously described by FURCHGOTT et al.[5]. Ventricles were suspended in an organ bath containing 20 ml of regular Ringer solution of the following composition (expressed in m*M*): NaCl, 103,4; KCl, 1,013; $CaCl_2$, 0.9009; CO_3HNa, 1.851. In the experiments with glucose, Ringer solution contained 10 m*M* of glucose. The solution also contained 10^{-5}g/ml ethylene diaminetetraacetic acid (EDTA). A mixture of 95% O_2 and 5% CO_2 was bubbled through the bathing solution, or 95% N_2

Table I. Effect of iodoacetate (IAA) on uptake and retention of H^3NE by isolated frog ventricle under aerobic conditions

N[a]	Glucose	Treatment	H^3NE present during incubation	H^3NE in tissue 45 min after washout in dpm/g[b]
6	Present	—	5 ng/ml (5 min)	174.966 ± 26.758
	Present	IAA (10^{-4}) (20 min)	5 ng/ml (5 min)	148.786 ± 24.655

[a] Number of experiments (paired). [b] Mean ± S.E.M. See text for further details.