tion in the mature one, followed by a decrease in the response to the higher PO_2 levels in the newborn animal.

The response to NE, tested at two levels of PO_2 (28 and 100 mm Hg), varied also as a function of the age of the animal (Table). The greater response was observed in the mature fetus at both low and high PO_2. The difference between the responses to NE at 100 and 28 mm Hg PO_2 (Δ) was also significantly larger in the mature fetus.

Our results are comparable with the report that the ductus of the fetal lamb increased its responsiveness to O_2 as a function of developmental age[6]. However, that preparation showed a distinct threshold for the response at a PO_2 of 65 mm Hg. In contrast, in our experiments, the guinea-pig ductus contracted gradually in response to any increase in O_2 above 0 mm Hg (95% N_2 and 5% CO_2) as shown in the Figure.

The temporal changes in ductal responsiveness to O_2 were characterized by a progressive increase with fetal maturation followed by a decline after birth. The increased responsiveness during the fetal period could depend upon maturation of a) specific receptors for O_2 or b) the ductal vascular smooth muscle. The first possibility was suggested in the report[7] describing dissociation of responses to O_2 and NE with advancing fetal age. Thus, oxygen receptors, with maturational characteristics different from those of NE receptors were postulated. Our results, without disputing the notion of differentiated receptors, support the second possibility namely, that the age dependent increase in responsiveness reflects the graded maturation of the vascular smooth muscle. This notion is based on our observation of a parallel increase in the contractile changes to O_2 and NE during fetal growth. The gradual decrease in the responses observed after birth may depend on involution of the ductal wall starting shortly after birth, as has been shown in the lamb ductus arteriosus[8].

Zusammenfassung. Die Wirkung von Sauerstoff und Norepinephrin auf die Kontraktionen des isolierten Ductus arteriosus des Meerschweinchens nimmt mit zunehmendem Alter des Feten bis zur Geburt zu und verschwindet kurze Zeit hernach wieder.

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Effect of Lithium on Brain Aconitase Activity

Although lithium salts are known to be effective agents against mood disorders[1,2], an explanation of lithium's mechanism of action in the treatment of manic-depressive psychosis is still lacking[3,4].

FORN and VALDECASAS[5] observed that a wide range of Li^+ concentrations inhibits rat and rabbit cerebral cortex adenyl cyclase in vitro. Recently, ABREU and ABREU[6] reported a highly significant in vivo activation of brain succinate dehydrogenase in mice treated with Li_2CO_3. The object of the present work was to find out whether any significant differences in brain aconitase (aconitate hydratase, E.C. 4.2.1.3) activity occur in mice on long term treatment with Li_2CO_3.

Material and methods. Male Swiss mice (26 g mean body weight) maintained in a standard balanced diet ad libitum were used throughout the experiment. One group of mice received as drinking water a solution containing 100 mg of Li_2CO_3/l. To the control group distilled water was given. After 108 days of treatment the animals were killed by cervical dislocation and the brains removed quickly. 10% brain homogenates were prepared immediately in ice cold distilled water and the aconitase activity was determined by a modification of the spectrophotometric method of RACKER[7]. The final volume was 3.0 ml including 1.5 ml of 0.06 *M* sodium citrate in 0.1 *M* phosphate buffer at pH 7.4 and 0.1 ml of brain homogenate added to start the reaction. After 10 min of incubation at 37 °C the reaction was stopped by the addition of 3.0 ml of 0.5 *M* $HClO_4$. A control was prepared for each sample by the addition of $HClO_4$ anf homogenate to the buffered substrate at time zero. Spectrophotometric determinations in the supernatants were made at 240 nm in a Shimadzu QV-50 spectrophotometer equipped with cells of 10 mm light path. The enzymatic activity follows a zero order kinetics and 1 unit is equivalent to a change in optical density of 0.001 in 10 min at 37 °C. Total proteins in the homogenates were determined by the biuret method of GORNAL, BARDAWILL and DAVID[8] using

Effect of Li^+ on mouse brain aconitase activity

Treatment	No. of mice	Body weight (g)	Aconitase (units/mg of protein)
Li_2CO_3	19	30 ± 0.7	218 ± 16
Controls	19	31 ± 0.6	233 ± 17

Each value represents the mean $\pm$ standard error of the mean.

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crystalline bovine plasma albumin as standard. The specific activity of aconitase was expressed as units/mg of protein. The Student's t-test[9] was used to evaluate the significance of the differences between Li_2CO_3 treated and control mice.

Results and discussion. The mean intake of water or Li_2CO_3 solution during the period of the experiment was the same (5.9 ml/mouse/day) in both groups of mice. This volume is equivalent to 19.7 mg of Li_2CO_3/kg of body weight/day, which is in the range of the dosage used in manic-depressive syndrome[2].

The results are summarized in the Table. Administration of Li_2CO_3 does not influence the final body weights of the animals (t=1.098, $P<0.5$). On the other hand, an inhibition of the specific brain aconitase activity was observed in Li_2CO_3 treated mice. This inhibition was found statistically significant (t=2.611, $P<0.02$). Attempts to demonstrate an in vitro effect of Li^+ were negative. Addition of Li_2CO_3 up to 0.5 mg to the incubation system did not change brain aconitase activity.

It is interesting to emphasize that the Li^+ effect on mouse brain aconitase was observed only in vivo as well as the action of this ion on brain succinate dehydrogenase activity[6]. Certainly, further studies are necessary to define whether the effects of Li_2CO_3 on these enzymes have any connection with the clinical effects of the drug.

Résumé. Nous avons déterminé l'activité spécifique de l'aconitase cérébrale des souris après une période de 108 jours de traitement avec du lithium (Li_2CO_3). Une inhibition significative de l'enzyme à été observée. D'autre part, nous n'avons trouvé in vitro aucun effet du Li_2CO_3 sur l'aconitase cérébrale.

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Compound 48/80 Decreases Adenosine 3′5′-Monophosphate Formation in Rat Peritoneal Mast Cells[1]

Adenosine 3′5′-monophosphate (cAMP) has been shown to influence the release of many compounds from a variety of cell types. In the majority of cases, e.g. thyroid hormone[2], amylase in the parotid gland[3], ACTH[4], growth hormone[5] and calcitonin[6], the release process appears to be mediated by an increase in cAMP levels. In contrast, agents which raise cAMP levels inhibit the antigen-induced release of histamine from the leukocytes of allergic individuals[7,8] and also the release of histamine from rat peritoneal mast cells by compound 48/80[9,10]. These latter observations suggested that the releasing agents in question might lower cAMP levels in these cell types. This possibility was explored by examining the effect of compound 48/80 on cAMP formation in purified rat peritoneal mast cells. Compound 48/80 at a concentration sufficient to release 50 to 60% of the total histamine present in the cells decreased the formation of cAMP by approximately 50%.

Materials and methods. Peritoneal cells were removed from female Sprague-Dawley rats and mast cells purified by repeated centrifugation of the cells for short time intervals as previously described[11]. The final cell preparation consisted of 65–90% mast cells. The formation of cAMP from (^{3}H)adenine[12,13] was measured by the method of Krishna et al.[14]. Cells were preincubated with (^{3}H)adenine (30 μc/ml) for 1 h, washed twice, resuspended with and without compound 48/80 and incubated for 15 min.

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Effects of compound 48/80 on histamine release and cAMP formation in rat peritoneal cells

Expt	48/80 (γ/ml)	Time (min)	Histamine Release (%)	Inhibition of cAMP[a] formation (%)
1–6	1.0	15	55.0 ± 9.5[a] (n = 8)	56.4 ± 14.3[a,b] (n = 12)
5,6	0.2	15	16.0 ± 4.4 (n = 4)	30.7 ± 11.5 (n = 4)
	1.0	15	52.3 ± 12.8 (n = 4)	53.3 ± 12.3 (n = 4)
7	1.0	1/12	69	58
	1.0	1/2	64	52
	1.0	2	72	60

[a] Average ± S.D. [b] Experiments were done in duplicate. Inhibition was calculated against the average of 2 controls for each experiment. The average difference between control values in 6 separate experiments was 12%.