tissue culture a decrease in cytotoxic indices (i.e. greater inhibition) in PEA pretreated animals has been found as compared to controls (Table).

Discussion. In the previous experiment when PEA was administered 6 weeks starting on the day of sensitization, the erythema of the tuberculine reaction in guinea-pigs was significantly decreased[3]. In our present experiment, the scheme of administration differed from the previous one. PEA was repeatedly administered prior to sensitization. The number of evaluated criteria was increased, as the skin test, its induration and inhibition of migration of macrophages are considered as the most significant features of delayed hypersensitivity. In this experimental design, PEA, contrary to the previous study, increased the erythema and induration of tuberculine reaction. There is also a satisfactory correlation between these in vivo tests and the test of inhibition of macrophage migration where the significant decrease of cell migration from explants was noted. From preliminary results not yet published PEA does not change the ability of the migration inhibitory factor (MIF) production by lymphoid cells in vitro. Our results suggest that PEA could play a modifying role in the course of development of certain immunological processes, and as the mechanism of action has not been clarified yet, further analytical studies are needed.

Zusammenfassung. Die Wirkung von N-(2-hydroxyethyl)palmitamid auf den Verlauf der Überempfindlichkeit des Spättypes in Meerschweinchen wurde verfolgt und festgestellt, dass die Verabreichung dieses Stoffes vor der Sensibilisierung eine Stimulation der Hypersensitivität bewirkt.

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Glutamate and GABA Levels and Glutamate Decarboxylase Activity in Brain Regions of Rats after Prolonged Treatment with Alkali Cations

Several reports have indicated the antagonistic effects produced by lithium and rubidium when administered to animals. Monkeys given chronic RbCl treatment showed changes in their behavior and EEG pattern opposite to those produced by LiCl[1]. Contrasting effects of lithium and rubidium on catecholamine metabolism were observed in rat brain[2]. Prolonged rubidium treatment resulted in excitation, aggression and fighting behavior in animals[1,3,4], whereas lithium reduced aggressive behavior and hyperactivity in animals[5–8]. It has, therefore, been suggested that rubidium might have therapeutic applications in affective disorders, particularly in depressions[9], and initial treatment has shown remarkable therapeutic response in depressed patients[10]. We have recently reported that repeated administration of low non-toxic doses of LiCl to rats produced differential changes in glutamate and γ-aminobutyric acid (GABA) levels in certain brain regions[11,12]. These observations, as well as the association of glutamate and GABA with the state of brain activity[13], led us to extend our previous work further[12], and to test the effct of other alkali monovalent cations, e.g. Na^+, Rb^+ and Cs^+, on the content of glutamate and GABA in several brain regions as well as on the enzyme glutamic acid decarboxylase (GAD) which forms GABA from glutamic acid.

Experimental. Male rats, 80–100 g from the Biodynamics Department Colony derived from Wistar stock, which had free access to Purina Laboratory Chow and water, were used. The treatment consisted of i.p. injections of 2 meq/kg of 1 *M* solutions of NaCl, RbCl or CsCl twice daily for 4 consecutive days. The last injection was administered 1 h before decapitation. The brain was removed without delay and different parts were dissected as described previous-

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Table I. Glutamate and GABA levels in brain regions of rats after prolonged treatment with alkali cations

Treatment	Glutamate (μmole/g fresh wt.) Cortex	Amygdala	Hypothalamus	Brain Stem	GABA (μmole/g fresh wt.) Cortex	Amygdala	Hypothalamus	Brain Stem
NaCl	13.6 ± 0.2 (7)	13.7 ± 0.4 (7)	11.0 ± 0.4 (7)	7.6 ± 0.3 (6)	2.1 ± 0.1 (7)	2.7 ± 0.2 (7)	4.3 ± 0.2 (7)	2.2 ± 0.1 (6)
RbCl	14.8 ± 0.4 (7)[b]	15.0 ± 0.4 (7)[b]	11.5 ± 0.4 (8)	8.3 ± 0.6 (6)	2.6 ± 0.2 (8)[a]	3.4 ± 0.2 (8)[a]	6.0 ± 0.3 (8)[c]	2.5 ± 0.3 (5)
CsCl	14.9 ± 0.4 (7)[b]	14.6 ± 0.3 (7)[a]	11.4 ± 0.3 (6)	8.0 ± 0.2 (6)	2.4 ± 0.2 (7)	3.0 ± 0.3 (6)	4.9 ± 0.3 (6)	2.5 ± 0.2 (5)

Each treatment (2 meq/kg) was given i.p. twice daily for 4 days. The last injection 1 h before sacrificing the rats. Means ± S.E. Number of samples in parentheses; each sample is composed of tissue pooled from 3 rats. [a] Difference from control rats (NaCl treated; see text) significant $P < 0.05$ (Student's t-test); [b] $P < 0.01$; [c] $P < 0.001$.

ly[12]. Each sample of cortex, amygdala, hypothalamus and brain stem (pons and medulla) was pooled from 3 rats. Glutamic acid and GABA were determined after separation by paper chromatography[14]. GAD activity was measured by a radiometric procedure[15].

Results and discussion. Table I shows that glutamate increased in the cortex and amygdala of rats administered with either RbCl or CsCl as compared to animals given the same dose of NaCl. GABA levels, however, increased in the cortex, amygdala as well as hypothalamus of rats treated with RbCl. Control rats received a similar treatment using NaCl. We have previously reported that animals injected i.p. with 2 meq/kg of either 1 *M* NaCl or isotonic saline solutions as well as rats introduced i.p. with a needle (sham) showed the same values of GABA and glutamate in certain brain regions[12]. Rats administered with RbCl appeared agitated compared to those receiving the same amounts of NaCl, KCl or CsCl. The weight gain of the animals of each group was not affected by the injections of these cations. The differential distribution of glutamate and GABA as well as the enzyme GAD in the brain strongly emphasises the importance of chemical and enzymatic analyses of well defined regions of the brain. The increased glutamate in the cortex and amygdala may be related, at least in part, to the increased blood glucose level known to result from rubidium and cesium treatment[16]. Increased incorporation of ^{14}C from labeled glucose into glutamate and GABA has been demonstrated in brain perfusion studies[17]. Lithium has also been shown to increase blood glucose level[18], but it is not known whether Li^+, Rb^+ and Cs^+ share a common mechanism in producing this effect. GABA is formed in the brain from glutamate[19] and this may explain the increase in GABA levels in the cortex and amygdala where the glutamate concentration increased in rats given RbCl. GABA levels did not change, however, in brain regions showing increased glutamate produced by CsCl treatment. This did not appear to be associated with changes in GAD activity since there were none under the experimental conditions (Table II). It should be noted, however, that the lack of change in GAD levels in postassium-treated rats is probably due to the fact that the concentration of K^+ in the brain is independent of its level in plasma[20]. Of particular interest is the observation that GABA content increased significantly ($P < 0.001$) in the hypothalamus of rats treated with RbCl despite the absence of change in the glutamate level in that region. Increased GABA concentration has been associated with a decrease in neuronal excitability (for review see Ref.[21]). On the other hand, high levels of GABA were found in brains of excitable rats[22]. The latter, and also our findings showing increased GABA concentration in the hypothalamus of rats given rubidium may be a metabolic effect non-specific to this ion. Rubidium which is taken up by the brain after chronic treatment[3] produces metabolic acidosis[23] and brain excitability[1,4]. The increased CO_2, associated with high brain activity, as well as the rubidium-induced acidosis lower the tissue pH and may decrease the activity of the enzyme GABA transaminase (pH optimum 8.2) and thus result in GABA accumulation[24]. The physiological action of GABA as a vasodilator substance[24] is presumably significant in the hypothalamus; known to be intimately involved in emotional behavior[25].

Resume. L'administration chronique des cations des métaux alcalins (Na^+, Rb^+, Cs^+) à les rats a provoqué la croissance des niveaux de glutamate et GABA dans certaines régions du cerveau. On n'a remarqué aucun changement en activité GAD de ces régions.

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Table II. Glutamic acid decarboxylase (GAD) activity in brain regions of rats after chronic treatment with alkali cations

Treatment	GAD activity (μmole/g fresh wt./h) Whole brain	Cortex	Hypothalamus
NaCl	36.3 ± 1.4 (8)	30.8 ± 0.4 (6)	62.4 ± 0.6 (6)
LiCl	36.3 ± 1.0 (8)	31.9 , 31.0	63.0 , 60.2
KCl	—	31.2 ± 0.6 (3)	61.0 ± 1.7 (3)
RbCl	—	30.6 ± 0.7 (6)	62.6 ± 1.3 (6)
CsCl	—	30.9 ± 1.5 (3)	62.4 ± 2.7 (3)

Each treatment (2 meq/kg) was given i.p. twice daily for 4 days. The last injection 1 h before sacrificing rats. Means ± S.E. Number of samples in parentheses; each sample is composed of tissue pooled from 3 animals.

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Non-Steroidal Anti-Inflammatory Drugs: Effects on the Utilization of Glucose and Production of Lactic Acid in Tissue Culture

Recently the finding that the non-steroidal anti-inflammatory drugs inhibit the production of prostaglandins E_2, and F_2 known as mediators of defensive reactions to noxious agents received much attention[1,2]. The drugs have been long recognized as multivalent substances which influence many different metabolic functions of the cell[3,4]. It has been repeatedly suggested that the effects of the drugs on the energy metabolism deserve special consideration[4-6].

In the present communication we report that various non-steroidal anti-inflammatory drugs at relatively low concentration have a profound effect on glucose utiliza-