The Effect of Reserpine and Chlorimipramine on Glycogen Content in Different Brain Structures of Rat

There is a large body of evidence that adenosine-3′5′-monophosphate (cyclic AMP) has an important role in brain function[1,2]. It is also known that psychotropic drugs affected cyclic AMP content in brain; chlorpromazine, haloperidol and other neuroleptic drugs blocked norepinephrine-induced increase of cyclic AMP[3,4]. Neuroleptic drugs are able to antagonize, the rise of cyclic AMP caused by psychotomimetic drugs[5]. There is suggestive evidence in the literature that changes in cyclic AMP in nervous system could be reflected on maniac-depressive states. ABDULA and HAMADAH[6] have suggested that intracellular deficiency of cyclic AMP might be related to a depressive state and marked increase leads to mania. It was found that depressed patients excreted less cyclic AMP in the urine thoran nmal subjects; while, on the contrary, marked increase of cyclic AMP appeared in urine of manic or hypomanic patients[7].

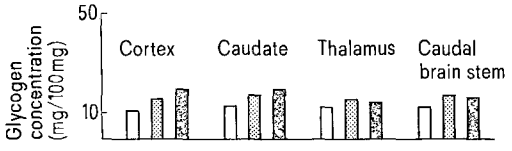

Fig. 1. The influence of reserpine (1.0 mg/kg) on the glycogen content in various brain structures of rat. Concentration of glycogen (in mg/100 mg of fresh tissue) is expressed as a difference of mean values between untreated (control) and treated animals. White, shadow and black columns represent the results obtained 24, 26 and 28 h after reserpine injection.

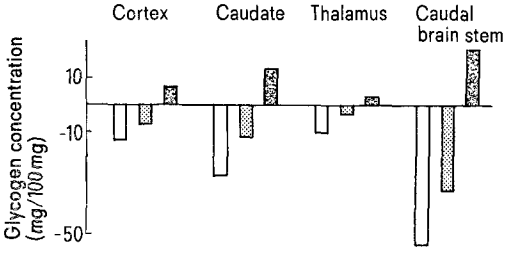

Fig. 2. The influence of chlorimipramine (25.0 mg/kg) on glycogen content in various brain structures of rat. Concentration of glycogen (in mg/100 mg of fresh tissue) is expressed as a difference of mean value between untreated (control) and treated animals. White, shadow and black columnes represent the results obtained 2, 4 and 6 h after chlorimipramine treatment.

The aim of this paper was to investigate the action of reserpine and the antidepressive drug chlorimipramine on glycogen content in rat brain, on the assumption that glycogen concentration in brain could be taken as an indirect parameter for cyclic AMP activity in nervous tissue. The control of glycogen concentration in the brain of experimental animals is a suitable model for the biochemical action and activity of cyclic AMP, since it is known that cyclic AMP exerted control over activities of both, the phosphorylase and glycogen synthetase systems[8].

Materials and methods. Male albino rats (230 to 280 g body weight) were divided in groups with 15 rats in each. 1. Saline-treated group (controls). Animals were injected with isotonic solution of NaCl and glycogen content was estimated after 24, 26 and 28 h, respectively. 2. Reserpine-treated group. These rats were treated with 1.0 mg/kg of reserpine and glycogen content was measured after 24, 26 and 28 h, respectively. 3. Chlorimipramine-treated group. Chlorimipramine in dose of 25.0 mg/kg i.p. was given to these animals and glycogen content was determined after 2, 4 and 6 h, respectively. 4. Reserpine-chlorimipramine combined treated group. Animals were treated by reserpine (1.0 mg/kg, s.c.) and 22 h later they were injected with chlorimipramine (25.0 mg/kg, i.p.) and glycogen was determined after 2, 6 and 6 h, respectively.

From the frozen brain tissue glycogen was extracted[9] and estimated[10].

Results and discussion. Reserpine markedly increased glycogen content in all brain structures (cerebral cortex, caudate, thalamus and caudal brain stem) of treated animals (Figure 1). All values were statistically significant in comparison with controls ($p<0.05$ and 0.001). The most pronounced effects of reserpine was found to be after 26 and 28 h. Contrary to reserpine, chlorimipramine exerted biphasic action on glycogen concentration in rat brain (Figure 2). Initially, i.e. 2 h after chlorimipramine administration, glycogen content was significantly decreased in all tested structures of brain ($p<0.05$). In contrary to this, 6 h after administration, glycogen content was markedly increased over control values in all structures ($p<0.05$), except in thalamus. Chlorimipramine de-

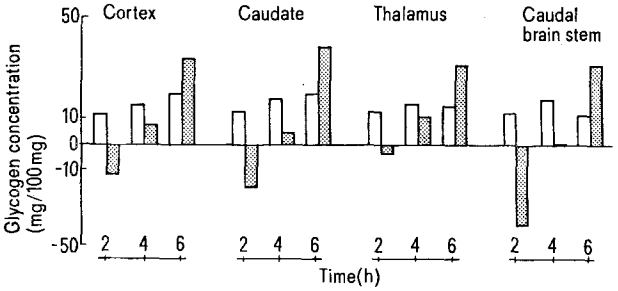

Fig. 3. Effect of chlorimipramine (25.0 mg/kg) on increased amount of glycogen in various brain structures of reserpinized animals (1.0 mg/kg). Concentration of glycogen (in mg/100 mg of fresh tissue) is expressed as a difference of mean values between untreated (control) and treated animals. White columns represent the results obtained in reserpine-treated group, and shadow columns those obtained in reserpine + chlorimipramine group.

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creased glycogen concentration in reserpine-treated animals (Figure 3), but only if it was measured 2 h after chlorimipramine injection (or 24 h after reserpine). 6 h after chlorimipramine (or 28 h after reserpine) glycogen content has found to be increased. In this time, glycogen concentration was nearly doubled compared with the sum of glycogen contents measured in the same time after treatment by reserpine or chlorimipramine. Actually, this could not be ruled out for thalamus since glycogen content was more than twice as high as the simple sum of effects, both of reserpine or chlorimipramine, when were given alone.

Many authors have shown that changes in cyclic AMP level can influence glycogen metabolism in rat brain. BRECKENRIDGE[11] found that increased level of cyclic AMP is followed by greater conversion of phosphorylase *b* to phosphorylase *a* and vice versa; phenobarbital treatment leads to a lowering of the level of cyclic AMP and to a decreased conversion of phosphorylase *b* to phosphorylase *a*. The glycogen concentration was decreased[12] at the time when the activity of phosphorylase *a* and cyclic AMP levels were markedly increased[13,14]. So it seems that glycogen concentration could be taken as indirect evidence for cyclic AMP activity.

On the other hand, changes in metabolism of catecholamines in the CNS may be followed by changes in central glycogen metabolism[12], and many centrally acting, which are able to modulate synthesis, release or breakdown of cerebral catecholamines, may also affect cerebral glycogen content. Results of our experiments have confirmed the finding of these authors that reserpine injection significantly increased glycogen content in CNS of rats. Our previous results showed that repeated injections of reserpine, in the course of 3 days, did not affect the glycogen concentration in rat brain[15]. In contrast to reserpine, chlorimipramine per se produced decrease of glycogen content, when it was measured 2 h after drug treatment. This could be explained by a blocking action of chlorimipramine on uptake of noradrenaline in presynaptic neurons and a consequently induced increase of cyclic AMP response to noradrenaline. Such a hypothesis, however, could not be taken as an explanation of increased glycogen levels which appeared 4 and 6 h after chlorimipramine treatment.

Imipramine has no effect on glycogen content in the brain of the mouse[12]. It also failed to show any effect on cyclic AMP content per se, but is able to counteract noradrenaline induced increase of c-AMP in vitro conditions in rats[3]. The divergence between our results and those above mentioned suggested different modes of chlorimipramine and imipramine action. It also can be explained by the differences in species or different experimental conditions. Combined treatment of rats by reserpine and chlorimipramine suggested an antagonistic action of the latter drug. This antagonism was evident only 2 h after chlorimipramine, i.e. 24 h after reserpine. After that time, antagonism disappeared and glycogen content was nearly doubled in all brain structures of treated animals. It is therefore very difficult to conclude either about antagonistic action of chlorimipramine on reserpine increased glycogen content, or about addative action of these two drugs. Perhaps it is better to conclude a dominant action of chlorimipramine in this particular experimental set up.

Résumé. La rézerpine (1 mg/kg) provoque une augmentation significative du taux de glycogène dans le cerveau du rat, surtout 26 et 28 h après le traitement. Contrairement à la rézerpine, la chlorimipramine (25 mg/kg) a une activité de base: 2 h après le traitement, le contenu du glycogène se réduit sensiblement, mais, 6 h plus tard, il augmente fortement, en comparaison avec les valeurs de contrôle. La chlorimipramine a le même effet dans le cerveau des animaux qui étaient 24 h préalablement traités à la rézerpine.

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Effect of Burimamide and Metiamide on Pentagastrin-Stimulated Gastric Acid Secretion and Gastric Mucosal Blood Flow in Cats

Although coming from the same chemical strain, the two histamine-H_2-receptor-antagonists, burimamide and metiamide, seem to be unequal brothers in some aspects: burimamide is generally regarded as inactive after oral administration, metiamide is well absorbed from the gastrointestinal tract[1]. Burimamide releases catecholamines[2,3], metiamide does not[3]. Burimamide inhibits gastric mucosal histamine methyltransferase; metiamide stimulates the enzyme at low concentrations and inhibits it at high concentrations[4]. The present paper describes the difference between burimamide and metiamide with regard to their inhibitory effects on pentagastrin-stimulated gastric acid secretion and gastric mucosal blood flow.

Methods. The experiments were done on cats (1.5–4.5 kg) of either sex under thiopental (60 mg/kg i.p.) and chloralose (30 mg/kg i.v.) anaesthesia. After a starvation period of 24 h, with free access to drinking water, the animals were provided with an acute gastric fistula from which the gastric juice was drained by gravity and collected in 15-min periods. Acidity of the gastric juice, the volume of which was read to the nearest 0.1 ml, was determined by endpoint titration to pH 7.0 with 0.1 *N* sodium hydroxide (Autoburette Radiometer, Copenhagen). Chloride concentration was determined argentometrically (chloride titrator CMT 10 Radiometer, Copenhagen). After a postoperative recovery period of 30 min, basal gastric secretion was collected for 1 h, after

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