The psilocybin hypersensitivity is also in agreement with the hypothesized brain monoamine supersensitivity in migraine-headache; nevertheless the interpretation is more difficult, because of scarse information about the pharmacological mechanism of this drug. However, psilocybin, besides possessing a chemical structure similar to 5-HT, exhibits, like LSD-25, mimetic and antagonist effects on 5-HT[16,17].

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[17] The authors are grateful to Sandoz Pharmaceuticals, Basel (Switzerland), for the supply of LSD-25 and psilocybin, and to Miss Una Hanratty for her assistance in the preparation of this paper.

Riassunto. Usando dosi suballucinogene di LSD-25 e di psilocibina è stato dimostrato che i soggetti sofferenti di cefalea essenziale sono più sensibili dei soggetti normali agli effetti psichici di questi farmaci. Questa ricerca sembra avvalorare l'ipotesi di una condizione di supersensibilità monoaminica cerebrale nelle cefalee essenziali.

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Some Cross-Protection Experiments on the Cholinergic Receptor of Frog Ventricular Strip

The pharmacological characteristics of cholinergic receptors in frog ventricle were first described by Clark[1-3]. The author found that acetylcholine (Ach) produces an inhibitory action on the contractile force. He observed that the antagonistic action of atropine (Atr) persists for a long time after repeated washing away of the drug. Ach did not increase the rate of recovery of the heart from Atr. At all Atr concentrations, the same maximal response could be elicited, provided the Ach concentration was made high enough. The effect of Atr on Ach seems to fit the classical description of competitive antagonism[4]. According to the mass law theory and occupancy assumption, when a maximal response is obtained in the presence of Atr the receptors should be occupied by Ach molecules and Atr molecules should have been displaced. Therefore, if the isolated tissue is washed many times by solution containing high concentration of Ach, it should have regained its original sensitivity to Ach. In fact, however, the decreased sensitivity persisted.

The aim of our study is to obtain further information by cross-protection experiments and to gain some insight into the mechanism of this anomalous antagonism.

Methods. The same method as described earlier[5] was used. In all experiments, Ach was applied at the concentration of 2 µg/ml. The contact time was 2 min. After this, the tissue was washed threefold with fresh solution and allowed to restore the normal ventricular function for about $^1/_2$ h. Atr was used in dose of 40 ng/ml. Phenoxybenzamine (Phe) was added to the bath at the concentration of 250 ng/ml. The contact time of antagonist with the tissue was 1 h. In cross-protection experiments[6], carbachol (Car) was used as the protective agent at the concentration of 20 µg/ml. This drug was simultaneously added to the bath with antagonist. The contact time of antagonist plus Car was 1 h. In such experiments Ach sensitivity of the strip was tested by 3 additions of agonist to the bath before the incubation. After the washout of antagonist plus Car, $^1/_2$ h was waited. Then, the Ach sensitivity was tested again. In each experiment group, the most obvious mean response induced by Ach was accepted as the 100% of Ach sensitivity. Other mean responses were evaluated according to this value. The numbers obtained in this way were graphically plotted versus the time (h).

Results. Ach induced a rapid and reversible negative inotropic effect. The sensitivity to Ach was tested during about 5 h. No any significant change was observed in the effect of Ach (Figure 1, no ago-antagonist) 6 strips were used ($n = 6$).

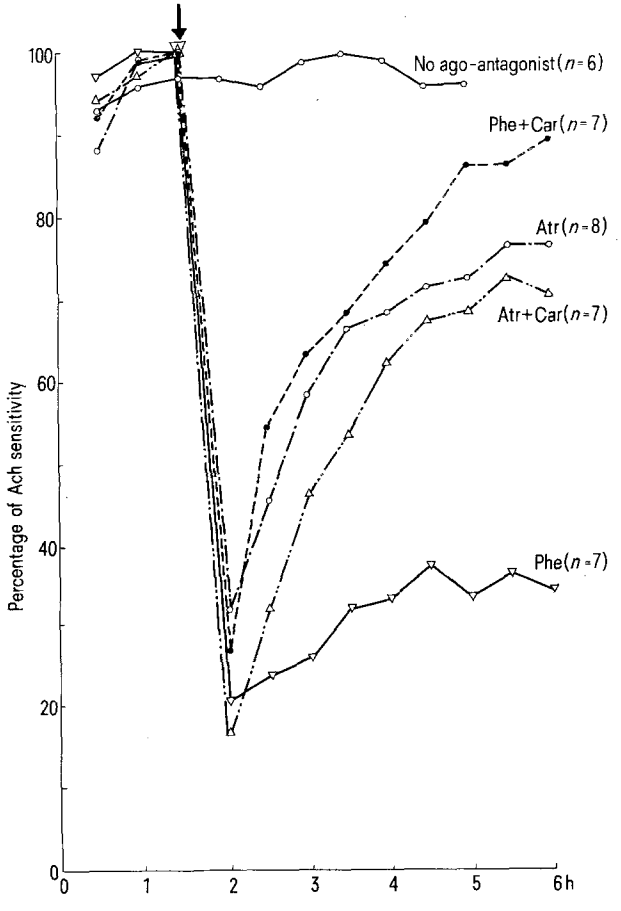

Fig. 1. ↓ 1 h treatment of the strips with antagonist (Phe, Atr) or antagonist plus Car, and then washing with fresh normal solution.

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In a separate group ($n = 8$) isolated strip was incubated with Ringer solution containing Atr. This drug did not produce any significant change on the contractile force and the spontaneous rhythm of the strip. Nevertheless, Ach sensitivity was prominently decreased during the oontact time. In spite of repeated washings and additions of Ach to the bath, the antagonistic action of Atr diminished slowly after the removal of this drug. Sensitivity did not return to its original level during 4 h. (Figure 1 Atr). 7 strips were treated with Phe. This substance did not cause any significant change on the physiological parameters of the strip. However, the effect of Ach was inhibited during the contact time (Figure 2, A). After the tissue was washed with fresh solution, decreased sensitivity did not show any significant change (Figure 1, Phe).

Seven strips were exposed to Atr with Car. The spontaneous activity of the strip was initially depressed but later normal rhythmic activity reappeared. Following the washing away of drugs, Ach sensitivity of the strip did not differ significantly from that which is observed in the experimental group where Atr is given alone (Figure 1, Atr + Car). In another separate experimental group, strips ($n = 7$) were treated with Phe and Car. The activity of preparation was initially depressed but later normal function was reestablished. After the washout, the initial antagonistic action of Phe against Ach was significant but it began gradually to diminish (Figure 2, B). At the end of the experiment, the tissue regained nearly its original sensitivity to Ach (Figure 1, Phe + Car).

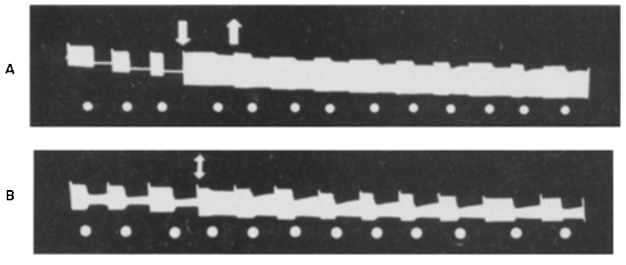

Fig. 2. A) ●, Ach 2 µg/ml; ↓, Phe 250 ng/ml; ↑, washing; B) ↕, Phe 250 ng/ml + 20 µg/ml Car-washing.

Discussion. In this study, we have observed that Car is unable to protect the cholinergic receptor against the action of Atr. However, the same substance prevented the appearance of long-lasting Phe block. These experimental findings led us to the conclusion that 2 antagonists may act on the different receptive sites of cholinergic receptor. Phe and Car probably react with the same receptive site. This may be the common cholinergic site on the receptor macromolecule. Atr possibly combines tightly with a separate special site of cholinergic receptor. This theoretical consideration based on the experimental findings is in agreement with the hypothesis proposed by GOLDSTEIN et al.[4]. In the model considered here for the cholinergic receptor, the binding of Atr and Ach to their respective sites mutually influences the affinity or intrinsic activity of each other. Such an action is reminiscent of the allosteric inhibition in enzymology[7].

Zusammenfassung. Bei Abnahme der Kontraktilität nach Azetylcholin wird am Frosch-Myokard-Modell nachgewiesen, dass Phenoxybenzamin den cholinergischen Rezeptor gegen Atropin «schützt», während Carbachol ohne Wirkung bleibt. Es wird angenommen, dass die beiden Antagonisten an verschiedenen Orten des cholinergischen Rezeptors wirken.

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Department of Pharmacology, Faculty of Medicine, Diyarbakir (Turkey), 7 May 1974.

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Stereotopography of the Prolactin Cells of the Rat Pituitary Gland

The relationship between secretory functions and ultrastructure is readily observed in many secretory cells. This applies not only to the synthesis of secretory granules or products but also to their packaging, transport and release. It is well known that granular endoplasmic reticulum surrounds the nucleus on the basal and lateral sides of pancreatic acinar cells[1,2], while the Golgi apparatus, in which maturation and packaging of secretory granules occurs, is located on the apical side of the nucleus[3,4]. The secretory granules then accumulate in the apical region of the cytoplasm and can be observed releasing their product by exocytosis into the lumen of the pancreatic acinus. This secretion scheme is typical for most protein secreting cells[1,3–5], but applies especially to those exocrine or endocrine cells which exhibit a high degree of polarization of their organelles.

A polarization of organelles within cells similar to that observed in the pancreas is often difficult to see in the cells of the anterior pituitary gland. This is probably due to the fact that pituitary cells do not form regular secretory units of structure comparable to the pancreatic acinus since the pituitary glandular associations are composed of several different kinds of cells[6]. Because of this, a three-dimensional analysis of the ultrastructural relationships of intracellular organelles in pituitary cells is justified. This would not only permit a better appreciation of the internal organization of cells, but would also give further information regarding the movement and release of secretory granules from the cytoplasm as well as the extent of functional polarization within the cells. Our previous observations[7] on the pituitary gland of lactating rats suggested that the prolactin cell would be the most suitable cell type for a study of this problem since they have a rapid turnover of secretory products.

Materials and methods. The pituitary glands were obtained from young, adult rats (Sprague-Dawley) which were in various stages of lactation. Details as to the experimental procedures used in our studies of prolactin

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