ments, rats were pretreated with ergocornine (methanesulfonate: 5 mg/kg i.p.), CB 154 (2-Br α-ergocryptine mesylate: 5 mg/kg i.p.)[11], or yohimbine HCl (Merck) (1 mg/kg i.p.), 20 min before morphine injections.

Results. Stereotyped movements. S 3608 induced automatic movements similar to those produced by apomorphine (sniffing, licking), but less important (biting reduced) (Figure). The stimulating effects of apomorphine appeared dose dependent. In grouped animals, the apomorphine effects (1.25 mg/kg) was greatly enhanced compared to that obtained in isolated rats. On the contrary, S 3608 at 80 mg/kg s.c. never induced a high intensity component of the stereotyped activity, as reported with Piribedil[12,13]. The intensity of stereotypy was not enhanced by increasing the dosage over 40 mg/kg, or by grouping animals. Furthermore, S 3608 even at 80 mg/kg did not induce agressivity in grouped rats, contrary to apomorphine at 2.5 mg/kg (Figure).

Rotations. S 3608 and Piribedil (25 mg/kg i.p.) induced a turning behaviour, contralateral to the left lesionned nigro-neostriatal tract. The total number of turns/rat ± SE were respectively in 30 min = 222 ± 92 and 214 ± 84 ($n = 6$). The same compounds administered at 6 mg/kg i.p., induced in 3 h a total number of rotations of 1151 (±370) and 957 (±261) for S 3608 and Piribedil, respectively ($n = 6$). The effect of the two substances appeared similar on the rotation model and was of a long duration.

Interaction with morphine catatonia. The catatonigenic ED_{50} of morphine alone was 8.2 mg/kg (6–11). After a previous treatment with S 3608 (8 mg/kg), the morphine induced rigidity was modified, and the ED_{50} value was 27.3 mg/kg (15–47) ($p < 0.05$). On the other hand, ergocornine, CB 154 and yohimbine gave evidence of antagonistic properties.. In these experiments, the new catatonigenic ED_{50} of morphine were respectively, 38 mg/kg (18–79), 23.5 mg/kg (13–40) and 23.3 mg/kg (12–43) ($p < 0.05$).

Conclusion. The central stimulating effect of S 3608 in the rat induced a stereotyped behavioural response, similar to that of apomorphine. The intensity of stimulation was self-limited and increasing the dosage of S 3608 above 40 mg/kg did not modify the response. The stereotyped response was only enhanced in higher doses in the case of apomorphine. On the contrary, these changes were not observed with S 3608 indicating the central stimulant effect is different in nature or intensity. S 3608 and Piribedil induced turning in rats, contralateral to a lesion in the substantia-nigra. The 2 compounds have a sustained effect, the central dopaminergic stimulant potency being comparable. S 3608 exerted a delay on the onset of morphine catatonia, modifying the ED_{50} of the analgesic. Ergocornine and CB 154 behaved as powerful antagonists on morphine catatonia, the former compound inducing peripheral neurovegetative signs, but the antagonistic effect of CB 154 was observed without any vegetative signs. Yohimbine modified the morphine rigidity, indicating that a block of the central sympathetic activity may be detected in the morphine model, as well as a strong direct dopaminergic stimulant effect.

The data support the hypothesis that S 3608 is a new direct central dopamine stimulant, different from apomorphine, qualitatively and quantitatively. In the rotation model, the potency of stimulation is similar to that of Piribedil. Further experiments are in progress to elucidate the mechanism of action of S 3608 on central dopaminergic and noradrenergic mechanisms.

Résumé. Le S 3608 [1-(coumaran-5-yl méthyl)-4-(2-thiazolyl) pipérazine] produit une important activation des récepteurs centraux de dopamine chez le rat. Les résultats permettent de formuler l'hypothèse d'un mécanisme d'action direct aux doses faibles.

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Ultrastructural Changes in the Neural Lobe of the Rat Pituitary Induced by Reserpine Treatment

Since 1952[1] and 1955[2] there have been reports on the inhibitory role of amines on the release of antidiuretic hormone. The histochemically demonstrable aminergic innervation of the neurosecretory cells in the supraoptic nucleus[3,4] or the direct aminergic innervation of the neural lobe[5] are both likely sites for influencing neuronal control. The observation that reserpine depletes neurosecretory granules from the neurons of supraoptic nucleus[4] led us to study further the effect of reserpine on the ultrastructure of the neural lobe.

The dosages of reserpine, Serpasil® (Ciba), were those generally used for depletion of amines from the brain tissue. Serpasil® was injected i.p. in 10 mg/kg, 5 mg/kg, 2.5 mg/kg, and 1 mg/kg dosages 24 h before killing the rats. 28 male albino rats of Sprague-Dawley strain, weighing about 200 g, were used for the present study. Gomori's chrom-alum haematoxylin staining[6] for neurosecretory material was performed on the neural lobes of 2 rats in every dosage group and on 4 controls. The other rats were perfused via the left ventricle with 2.5% glutaraldehyde 0.1 *M* phosphate buffer solution for 15 min. The neural lobes were then excized and immersion fixed for 4 h in the same fixative, postfixed in 1% OsO_4 for 1 h, dehydrated and embedded in Epon-Araldite. The ultrathin sections were stained with lead citrate[7] and uranyl acetate[8].

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Light microscopically, no detectable staining of neurosecretory material was observed in the neural lobes of any of the reserpine-treated rats as compared with the controls, which stained for the neurosecretory material. The neurosecretory endings showed vacuolization.

Ultrastructural changes observed in the neural lobes of the reserpine-treated rats were conspicuous, being most advanced in the rats which had received 10 mg/kg of reserpine. The number of neurosecretory granules of 1500–2500 Å diameter had strikingly decreased in the nerve terminals (Figure 1), while in the control animals the nerve terminals contained large numbers of granules with different shades of electron opaque cores (Figure 2). In particular, the large endings, Herring bodies, exhibited membraneous lamellary bodies and lysosome-like organelles (Figure 3), which are not usually found. The number of clear synaptic-like vesicles of 450 Å diameter was increased, as seen in Figure 1. Glycogen particles were observed in the nerve terminals of the reserpine-treated rats.

The pituicytes, which under normal conditions show relatively few cell organelles and are mainly devoid of

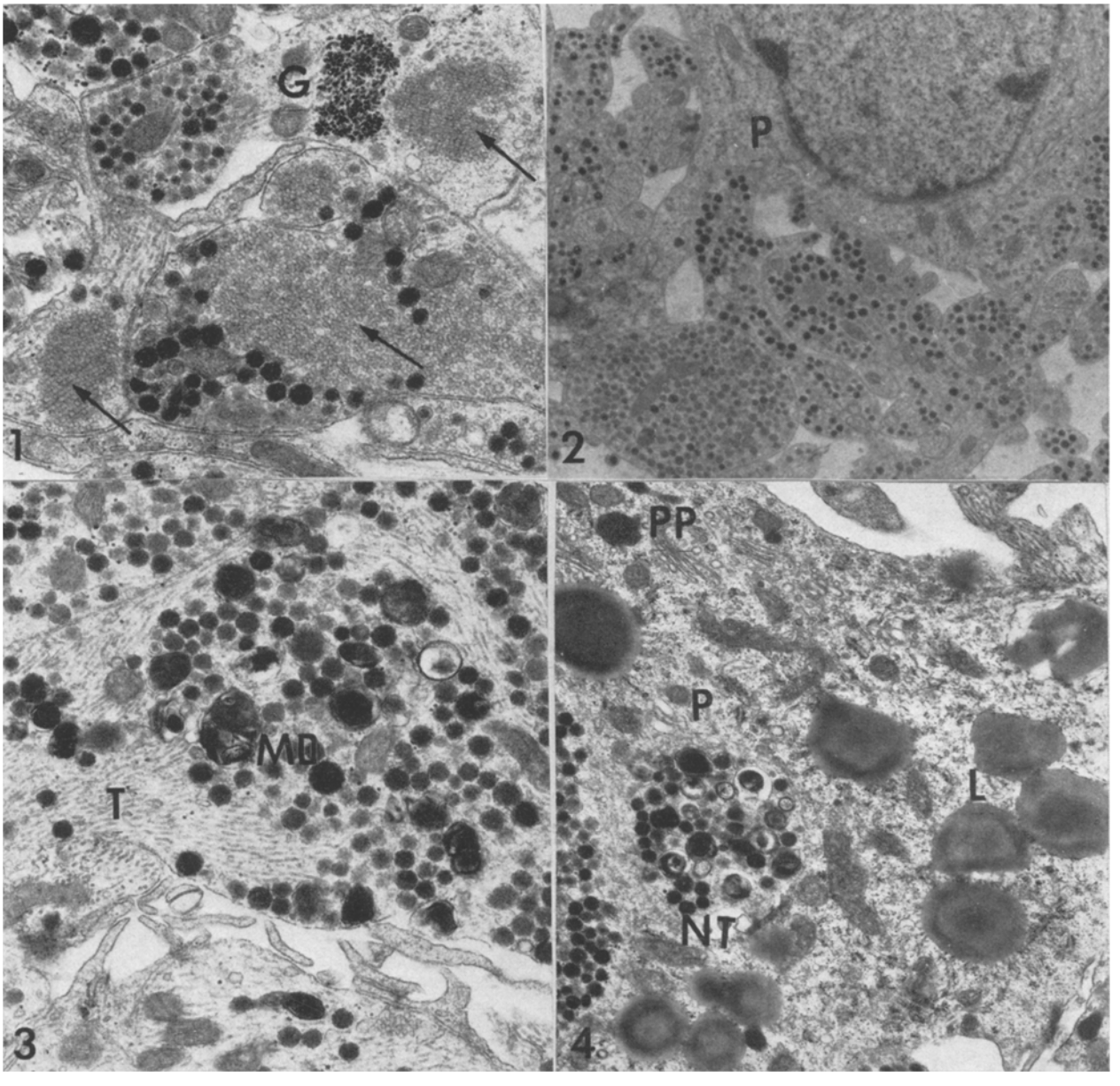

Fig. 1. Electron microscopic view of nerve terminals from the neural lobe of a rat treated 24 h before with 10 mg/kg reserpine. Note the disappearance of the large hormone storage granules, and the appearance of large amounts of small clear vesicles (pointed by arrows). The axons contain glycogen (G). × 16605.

Fig. 2. In electron microscopic view of the neural lobe of a control rat the nerve terminals contain abundantly hormone granules of different electron density. A pituicyte with scanty cell organelles is seen in the upper corner. × 5100.

Fig. 3. A large neurosecretory terminal of a rat treated with 5 mg/kg reserpine. Vacuoles, lamellary bodies (MB), lysosome-like bodies and an increase in tubular structures (T) were common features. × 16605.

Fig. 4. A nerve terminal (NT) is seen invaginated in the cytoplasm of a pituicyte (P), which shows a processus (PP) and large lipid droplets (L) in its cytoplasm. × 16605.

lipid droplets, revealed numerous large lipid droplets after reserpine treatment, see Figure 4. The pituicytes had formed processes which surrounded the neurosecretory axons. Some of the terminals were found to be invaginated in the cytoplasm of the pituicytes (Figure 4).

The doses of reserpine used in the present study: 1, 2.5, 5 and 10 mg/kg, which are generally used on experimental animals to deplete the amines, were found to produce marked ultrastructural changes in the nerve terminals, suggesting a vigorous release of hormone granules. Due to the depletion of granular material, the reaction of the pituicytes seemed well-adapted. It has been suggested that the pituicytes are involved in the secretion process of the hormone release[9]. The phagocytosis of the nerve terminals by the pituicytes has been observed, e.g. after stalk transsection leading to an increase in the lipid droplets[10, 11]. The conspicuous finding of enhanced clear small vesicles in the axon terminals suggests their participation in the release of hormones in some way. Their origin, content and function, and especially their relation to the hormone storage granules, is still unsettled[12]. If the hormone release induced by reserpine treatment is caused by inhibition of the amine-ergic control of the hormone release, is it due to other pharmacological properties of reserpine, e.g. toxic or lytic properties of the dosages used, or does reserpine interact in the granular bonding mechanism? This question remains to be answered. To differentiate the possible mechanisms, studies with different dosages of reserpine combined with in vitro studies and using chemical sympathectomy to exclude the effect of aminergic innervation, are in progress.

Summary. The doses of reserpine, which are generally used to deplete amines from the nervous tissue caused marked ultrastructural changes in the neural lobes of reserpine treated rats. The findings suggested depletion of neurosecretory granules, increased lysosomal activity and changes in the pituicytes.

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Unusual Mitochondria in Human Skeletal Muscle

During recent years, many atypical mitochondria have been reported, and several pathological conditions are known in which mitochondrial alterations have been observed[1-11]. Megamitochondria, for instance, characterized by an enormous dimension of the matrix and a reduced number of cristae have been found in a nephrotic syndrome, idiopathic cardiomyopathy, and can be experimentally induced in hepatocytes of rodents after feeding ethidium bromide or chloramphenicol[12, 13].

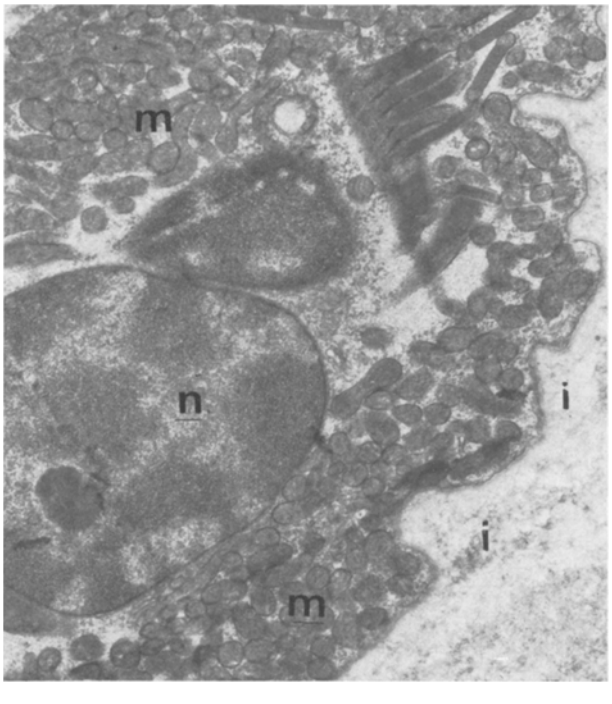

Fig. 1. Tis micrograph presents the subsarcolemmal part of a muscle fibre which contains a nucleus (n) and abundant mitochondria (m) partly showing a drumstick-like shape. i = interstitial space. × 12,500.

The purpose of this communication is to report on a hitherto unknown morphological phenomenon of mitochondria which has been observed in one case of systemic sclerosis (scleroderma) during electron microscopical studies of human skeletal muscle.

Material and method. The patient was a 40-years-old male who showed a generalized cutaneous scleroderma of at least 2 years duration. The specimens of the muscle biopsy were prefixed in buffered glutaraldehyd and postfixed in buffered OsO_4-solution. Ultrathin section were investigated electron microscopically after staining with uranyl acetate and lead citrate solutions.

Results and discussion. The muscle cells investigated in this case are characterized by the presence of abundant mitochondria, most of which are located near the sarcolemma surrounding the nucleus (Figure 1). The mitochondria – usually spherical or somewhat elongated – are located very close, so that no other organells can be seen. They

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