norethandrolone even significantly reduced the inflammatory reaction ($p < 0{\cdot}01$). As judged from the thymus weight, both steroids caused lympholysis, although norethandrolone had a much weaker effect than cortisol. The marked atrophy of the adrenal glands caused by cortisol was not significantly influenced by norethandrolone. On the contrary, the latter hormone given alone slightly diminished the adrenal weight, with a reduction in sudanophilia.

Adrenalectomy did not change the animals' response to norethandrolone, even as regards its anabolic property; the loss of body weight caused by cortisol, which is relatively higher after adrenalectomy, was effectively prevented by norethandrolone.

Effect of cortisol and norethandrolone upon the growth of a transplanted fibrosarcoma (Table II). The effects of both hormones on body and thymus weights obtained here are similar to those reported in the previous experiment. The higher gain in body weight is attributable to the longer period of treatment. Tumor weight revealed that the neoplastic growth responded to the steroid treatment exactly as did the inflammatory reaction.

Discussion: Analysis of our results reveals a remarkable degree of uniformity in the responsiveness of intact and adrenalectomized animals to treatment with cortisol and norethandrolone. The remarkable tolerance of adrenalectomized rats for norethandrolone was unexpected, since another anabolic hormone, the pituitary growth hormone, is very toxic in the absence of adrenals[11]; thus, the presence of that gland is not indispensable for the occurrence of tissue anabolism.

It is noteworthy that two somewhat metabolically opposed steroids exerted an additive effect upon the evolution of inflammation and cancer. This influence seems to be a direct one, at least in the case of inflammation, since it is also demonstrable in the absence of adrenals. Like other testoids[12], norethandrolone causes a weak, but direct, involution of the thymus. At the dosage used, the hormone also exhibited progestative properties, with definite hypertrophy of the preputial glands and external genitals; this effect was not prevented by cortisol treatment.

In the present study, the inhibitory action of cortisol upon the growth of the fibrosarcoma was highly significant ($p < 0{\cdot}01$). These results may not agree with other reports[13,14], but the effect of the corticosteroid upon the growth of transplantable tumors largely depends upon the origin of the neoplasm and the modality of treatment[15]. Here, the rate of the tumor growth singularly compares with the reaction of the connective tissue.

These observations may provide useful therapeutic applications, especially when anti-inflammatory corticosteroids are to be administered in high doses and for a prolonged period. In such instances, the conjoint treatment with norethandrolone may be indicated until the advent of a more specific anti-inflammatory steroid.

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Résumé

Le norethandrolone administré chez le rat intact ou surrénalectomisé se montre très efficace à prévenir la perte de poids causée par le cortisol. Cet antagonisme, toutefois, n'est pas démontrable en ce qui concerne l'effet anti-inflammatoire, la diminution de la croissance tumorale et l'atrophie du thymus et de la surrénale dus au cortisol. En outre, le norethandrolone présente à lui seul des propriétés anti-inflammatoires et thymolytiques, plus spécialement chez l'animal intact.

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The Action of 5-Hydroxy-DL-Tryptophan and 5-Hydroxy-Tryptamine on the Cortical Electrical Activity of the 'Midpontine Pretrigeminal Preparation'

In order to study the action of 5-hydroxy-tryptophan (5HTP) and 5-hydroxy-triptamine (5HT) on the central nervous system, we followed the EEG changes induced by these drugs on the midpontine pretrigeminal cat with or without midbrain hemisection. The drugs were injected into the carotid artery. Electro-cortical activity, arterial blood pressure, and carotid blood flow (Rein's Thermostromuhr) were simultaneously recorded.

The main results were as follows:

(1) The EEG pattern of the midpontine pretrigeminal preparation is characterized by the low voltage fast rhythms which are considered typical of the waking state[1]. 5HT (2–80 μg) slowly injected into the carotid artery – the controlateral artery being closed – never changed this pattern, neither modified, at least in some of our experiments, the carotid blood flow and the arterial blood pressure.

On the contrary, 5HTP (8–20 mg) injected in the same way, brought about high voltage slow EEG rhythms similar in every respect to those produced by thyopental. This pattern, which lasted more than 30 min, was reversible and was easily activated by olfactory and visual stimulations. In many instances, 5HTP, at doses active on the EEG, was ineffective on the carotid blood flow and the arterial pressure.

(2) 5HTP (8–20 mg) injected into the carotid artery – the controlateral artery being open – yielded a clear EEG asymmetry, the cerebral hemisphere on the side of the injection showing a degree of synchronization more pronounced than the one of the opposite hemisphere (Fig.). This means that the EEG effect of 5HTP (a) is most likely to start just at the first passage of the drug into the cerebral circulation, and (b) must be largely independent of extra-cerebral metabolic products of 5 HTP, which ought to impinge symmetrically upon the nervous structures. At lower dosage (4–8 mg), 5HTP produced a latent asymmetry which was revealed by small doses of thiopental (2–3 mg/kg i. v.) which produced a higher degree of synchronization over the hemisphere ipsilateral to the injection of 5HTP. Whatever the doses of 5HTP used, we never obtained, an EEG asymmetry opposite in sign to that described above.

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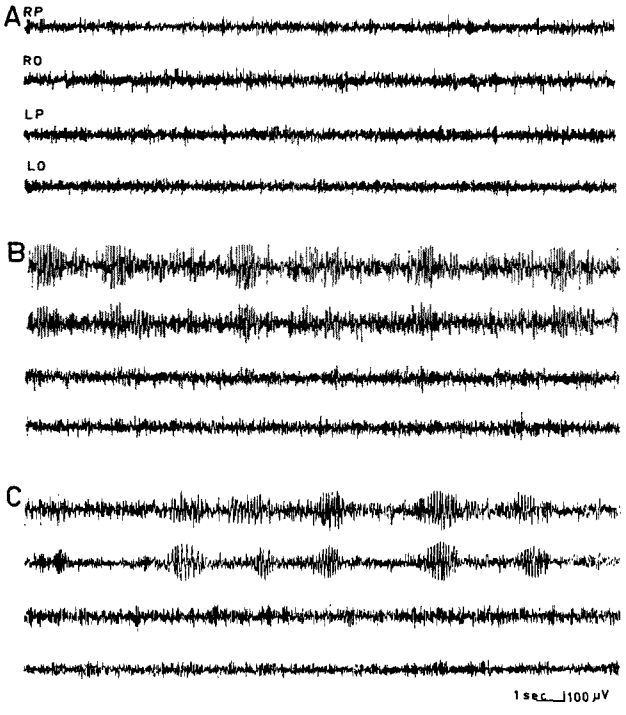

Effects of 5HTP on the EEG of the midpontine-pretrigeminal cat.

(A) EEG pattern symmetrically activated, 2 h after midpontine transection.

(B) Clear EEG asymmetry produced by 1 mg of thiopental injected into the right carotid artery, the controlateral artery being open: only the hemisphere on the side of the injection shows synchronization.

(C) The same EEG pattern produced by 20 mg of 5HTP injected as in (B).

(3) The EEG patterns of the midpontine pretrigeminal cat following mesencephalic hemisection have long periods of asymmetry; in fact the hemisphere overlying the section shows marked synchronization, while the other hemisphere is desynchronized[2]. Olfactory stimulation gives an arousal reaction. In this preparation, 5HT (1–4 μg) injected into the carotid artery – the controlateral artery being closed – frequently produced a clear arousal reaction, which ran independent of changes in the cerebral blood flow, at least when they were recorded at carotid level. In contrast, 5HTP (5–10 mg) not only brought about a symmetric synchronization, but it also frequently blocked the arousal reaction from olfactory or visual stimulation.

Our results are in part at variance with those obtained by other research workers (GANGLOFF and MONNIER[3]; CREPAX and INFANTELLINA[4]; MANTEGAZZINI[5]; ROTHBALLER[6]; MONNIER and TISSOT[7]; COSTA and RINALDI[8]).

A full discussion of our results and a tentative explanation of the discrepancies between our data and those of the above mentioned investigators will be given in the paper *in extenso*. It is evident, however, that differences in animal species, route of administration of the drugs, and experimental methods may be responsible for different results and hence for different interpretation of the physiological action of 5HT and 5HTP on the central nervous system.

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Riassunto

Il 5HTP, direttamente iniettato nel circolo cerebrale, produce un quadro elettroencefalografico di sonno, indipendente da modificazioni di flusso nel circolo cerebrale e da eventuali metaboliti che si formano al di fuori del cervello. La 5HT, iniettata nelle stesse condizioni, o è senza effetto o dà una reazione elettroencefalografica di risveglio.

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Glutaminase I Activity in Guinea Pig and Rabbit Liver and Kidney Tissues

Phosphate-activated glutaminase (Glutaminase I) has been demonstrated in rat and mouse brain, spleen, liver and kidney and in brain and spleen of rabbit and guinea pig; but in extracts of guinea pig, rabbit liver, kidney tissue, and of mitochondrial preparations, the phosphate activation of glutaminase activity has as yet not been demonstrated[1]. The object of the present report is to demonstrate glutaminase I activity in guinea pig and rabbit liver and kidney tissues.

Methods: Tissue extracts and mitochondrial preparations were made according to the procedures of ERRERA *et al.*[1], and the methods of SCHNEIDER[2] were followed when sucrose was employed for the preparation of mitochondria. The enzyme activity was determined by measuring the ammonia formed in presence of (5×10^{-3} *M*) L-glutamine (0·05 *M* Veronal Buffer pH 7·2 or 0·05 *M* Veronal Acetate Buffer pH 8·4). Incubations in Warburg's vessel at 37°C for 1 h, ammonia estimated by the method of BRAGANCA *et al.*[3]. Enzyme preparations equivalent to 50 mg of tissue (wet weight) for kidney and 100 mg for liver in all cases.

Results and Discussion: Glutaminase activity of tissue extracts and mitochondrial suspensions of guinea pig and rabbit liver and kidney, as shown in Table I, indicates that phosphate activation is most prominent at pH 7·2, especially with the mitochondrial system. The effect of DL-glutamic acid (Table I) on the enzyme activity in absence of any added phosphate showed a slight inhihtion with kidney tissues, while the liver enzyme was not found to be inhibited in accordance with KREBS[4]. However, in the presence of added phosphate, the inhibition of glutamic acid in all the tissue preparations was most significant. Varied concentration of phosphate showed (not shown in the Table) the phosphate-glutaminase activity curve to assume a flattened plateau after reaching the maximum of the optimal phosphate concentration of 0·2 *M* with no further increase in enzymatic activity.

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