CHANGES IN SOME CENTRAL EFFECTS OF SEROTONIN IN CATS AGAINST THE BACKGROUND OF ANTIDEPRESSANTS

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In experiments on cats, imipramine and chloracizine* potentiate the autonomic (vomiting effect) and behavioral (suppression of conditioned-reflex fear) responses of serotonin but have no significant effect on its motor effects (blocking of the glossomandibular reflex).

Investigators are nowadays inclined to consider that serotonin-positive properties of the tricylic antidepressants are among the principal factors determining their specific psychotropic activity [17]. However, as well as evidence of the potentiation of serotonin effects by antidepressants [2, 16, 18], there is also evidence that they possess serotonin-negative properties [12-14]. In particular, the authors have shown in experiments on rats that imipramine and chloracizine* can block serotonin-sensitive structures in some functional systems of the brain.

Because of the marked differences in the pharmacological properties of the antidepressants, their metabolism, and in their distribution in the brain of different species of animals [1, 8], it was decided to investigate the effect of imipramine and chloracizine on the central effects of serotonin in experiments on cats.

EXPERIMENTAL METHOD

The effect of imipramine and chloracizine on motor (depression of the glossomandibular reflex), autonomic (the vomiting effect), and behavioral (suppression of conditioned-reflex fear) reactions of serotonin was studied in cats.

The glossomandibular reflex was recorded mechanographically [7]. Previous work [9] showed that inhibition of the reflex by serotonin is due to its action on serotonin-sensitive structures in the caudal part of the brain stem. In the present experiments the degree of inhibition of the glossomandibular reflex by serotonin (220 μg, intravenously) was compared at various times after administration of the antidepressants (2 and 20 min, 2 h).

In the study of the emetic action of serotonin, its precursor 5-hydroxytryptophan (5-HT) was used. The vomiting developing in this case was due to excitation of the central serotonin receptors [3, 12]. 5-HT was injected intraperitoneally in a subthreshold dose (5 mg/kg) into intact and experimental cats. An initial water load was given. The presence of a vomiting effect was tested for 90 min. The number of positive effects in the group of animals receiving antidepressants was compared with the control.

*2-Chloro-10-(3-dimethylaminopropronyl)phenothiazine.

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Conditioned-reflex fear was produced by the method described by Il'yuchenok and Eliseeva [6]. The intensity of the fear response was assessed by a 4-point scale [5]. Depression of the fear response by 5-HT (15 mg/kg) was expressed in per cent. A previous investigation showed that endogenous serotonin formed by 5-HT has a depriming effect on negative emotional responses in cats as the result of interaction with central serotonin structures [5]. The blocking action of 5-HT at the beginning of the experiment was compared with its effect at various times after injection of imipramine and chloracizine (30, 60, 90, and 120 min).

Imipramine and chloracizine were injected intravenously in doses not affecting the parameters studied when administered alone.

The effects of imipramine on serotonin breakdown was determined by the method described by Khavronina and Gilev [10].

EXPERIMENTAL RESULTS

Imipramine (2 mg/kg) and chloracizine (2 and 5 mg/kg) had no significant effect on the inhibition of the glossomandibular reflex by serotonin, although in some cases a tendency was observed for the effect of serotonin to be reduced or increased.

The emetic action of serotonin was potentiated by imipramine and chloracizine. The most marked effect of potentiating serotonin was observed when imipramine was given repeatedly (1× 4 mg/kg daily for 5 days), when injection of 5 mg/kg 5-HT induced vomiting in all 5 animals, whereas before administration of imipramine the same dose of 5-HT had been ineffective in every case.

The blocking effect of serotonin on the fear response in the cats was considerably increased by both antidepressants. For instance, before injection of imipramine (1 mg/kg), 5-HT (15 mg/kg) depressed the fear rseponse by $45 \pm 6.2\%$, compared with $90 \pm 6.3\%$ after injection of imipramine ($P < 0.001$). The corresponding figures for potentiation of the blocking effect of 5-HT by chloracizine (2 mg/kg) were 45 ± 6.2 and $98 \pm 1.7\%$ ($P < 0.001$). Potentiation of the effect of 5-HT by the compounds began to be observed 30 min after its administration and continued for more than 2 h.

The tested compounds thus potentiated the autonomic and behavioral effects of serotonin but had no marked action on the motor responses to it. The writers' previous experiments on rats showed that imipramine (20 mg/kg, intraperitoneally) and chloracizine (20 and 70 mg/kg, intraperitoneally) block the motor and behavioral responses evoked by serotonin. Differences in the character of action of the antidepressants on the central effects of serotonin in rats and cats probably cannot be attributed to species-specificity of the serotonin receptors, because, as the results of the previous investigations showed, the central serotonin-sensitive structures in different species of animals do not differ from each other significantly in their sensitivity to blocking agents [4]. It could be postulated that this feature of the action of the antidepressants is due to differences in the antimonoamine-oxidase activity of imipramine and chloracizine in different species of animals.

To shed light on this problem, additional experiments were carried out to study the effect of imipramine and chloracizine on the breakdown of serotonin by cat and rat brain homogenates. The compounds were used in doses identical with those used when their action of the central effects of serotonin was tested in animals of these species.

In the experiments in vitro only chloracizine inhibited (by $47.3 \pm 12.5\%$; $P < 0.05$) the inactivation of serotonin by cat brain homogenates. In the experiments in vivo, on the other hand, neither imipramine nor chloracizine had any significant effect on the destruction of serotonin by cat and rat brain homogenates.

Consequently, the different effects of the antidepressants on the central effects of serotonin in rats and cats can hardly be attributed to differences in the action of these compounds on destruction of the amine. It is most likely that these differences are due to the unequal action of the antidepressants on nonspecific binding of serotonin in animals of this species [15, 16].

Hence, when the serotoninergic component in the action of antidepressants is assessed, not only their effect on serotoninergic structures in different functional systems of the brain, and on serotonin metabolism, but also the change produced by them in nonspecific binding of the amine in animals of different species must also be taken into account.

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