EFFECT OF TRANQUILIZERS AND ANTIDEPRESSANTS ON SUMMATION OF HETEROMODAL IMPULSES

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The effect of tranquilizers (chlordiazepoxide, diazepam) and an antidepressant (imipramine) on impulse summation in the CNS during photic, acoustic, and nociceptive stimulation was studied in experiments on rats. These substances in relatively small doses were found to potentiate impulse summation during nociceptive stimulation, but in large doses they weaken it for other types of stimulation. These substances weaken summation of impulses in spinal cats and rabbits during nociceptive electrical stimulation of the hind limb and direct stimulation of the thalamic centers in cats.

In a study of the effect of tranquilizers (meprobamate, chlordiazepoxide, diazepam) and antidepressants (imipramine, nialamide, tranylcypromine) with one impulse summation in the CNS during nociceptive (electrical) stimulation the writer showed [1] that these substances, in relatively small doses, potentiate the ability of the brain centers to summate subthreshold stimull, and weaken this ability only in large doses.

It was therefore decided to study whether tranquilizers and antidepressants have a positive effect on the summation of impulses of a different modality and, in particular, during photic and acoustic stimulation.

EXPERIMENTAL METHOD

Since as a rule it is impossible to investigate the summation of photic or acoustic stimuli in experimental animals with respect to unconditioned responses, a conditioned reflex technique was used. The conditioned stimuli were photic (flashes) and acoustic (buzzer) stimuli, generated with a certain frequency, amplitude, and duration. An electric current was applied as the unconditioned stimulus. The experiments were carried out on rats by Courvoisier's method [2], i.e., the animal was placed in a chamber with the floor constituting one electrode and with a vertical rod in the center. In response to electrical stimulation the animal jumped on the rod and so avoided further stimulation. Simultaneously with the electric shock, photic or acoustic stimulation of assigned frequency was applied. After several training sessions a conditioned avoidance reflex was formed in the rats; i.e., they jumped on the rod after a certain number of photic or acoustic stimuli without reinforcement by the unconditioned stimulus; the number of these stimuli was used as the criterion of the effect. The largest number of photic or acoustic stimuli was 10 at a frequency of 2/sec. The number of stimuli in response to which an unconditioned avoidance response occurred (jumping on the rod) was determined.

The tranquilizers used were chlordiazepoxide (Elenium) and diazepam (Seduxen), and the antidepressant was imipramine. Morphine also was used for reference, for it has a marked effect on impulse summation in the CNS.

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TABLE 1. Doses (in mg/kg) in which the Drugs Tested Induce Summation of Impulses During Heteromodal Stimulation

Name of drug	Nociceptive		Photic		Acoustic	
	potentiation	weakening	potentiation	weakening	potentiation	weakening
Chlordiazepoxide	1—2	4,0	—	4,0	—	4,0
Diazepam	0,1—0,2	1,25	—	1,25	—	1,25
Imipramine	0,1	1,5	—	1,5	—	1,5
Morphine	—	0,5	—	0,5	—	0,5

EXPERIMENTAL RESULTS

In relatively small doses, in which they potentiate the summation of nociceptive stimuli, chlordiazepoxide, diazepam, and imipramine had no effect on the summation of photic and acoustic stimuli. However, in doses in which these substances weaken the summation of nociceptive stimuli they also weakened the summation of photic and acoustic stimuli (Table 1).

To analyze the results it was important to determine whether tranquilizers and antidepressants produce a stimulant effect on impulse summation at the spinal cord level. For this purpose, a series of experiments was carried out on spinal rabits and cats. The spinal cord was divided under ether anesthesia at the level of the lower thoracic segments. One hind limb was stimulated electrically through needle electrodes inserted beneath the skin of the foot. The frequency of the stimuli was 10 or 20/sec,* their amplitude 8-10 V, and their duration 0.5 msec. Using an electronic counter the number of stimuli in response to which reflex flexion of the stimulated limb developed was recorded automatically. Movement of the limb was recorded by means of a photoelectric cell. The total number of stimuli did not exceed 100.

In the spinal animals chlordiazepoxide, diazepam, and imipramine caused weakening of impulse summation in doses 2 to 4 times greater than those for which summation of impulses was facilitated during nociceptive stimulation in intact rabbits. Morphine weakened impulses in spinal animals in doses two to four times greater than those for which summation of impulses in intact rabbits was weakened during nociceptive stimulation. The doses of the drugs for which weakening of summation of impulses was observed in spinal animals are given below (in mg/kg): chlordiazepoxide 6.0, diazepam 0.2-0.4, imipramine 0.3, morphine 1-2.

Since in cats it is impossible to investigate impulse summation in the CNS during nociceptive stimulation, for they respond to the nociceptive stimulation by a generalized violent reflex movement, a series of experiments was carried out on cats with direct stimulation of one of the nonspecific thalamine nuclei (n. medialis dorsalis) participating in formation of the response to nociceptive stimulation, instead of stimulation of the peripheral receptors and nerve fibers. The thalamic centers in the cats were stimulated directly through implanted electrodes at a frequency of 100-200/sec until a vocal (mewing) and general motor response (restlessness) appeared after a time not exceeding 10 sec.

Under these conditions chlordiazepoxide, diazepam, and imipramine suppressed the vocal and general motor responses of the cats in the same doses as those in which they intensified the summation of impulses during nociceptive electrical stimulation of the hind limb of an intact rabbit. For comparison, morphine was tested under the same conditions. The tests showed that doses of morphine followed by weakening of impulse summation during direct stimulation of the thalamic centers in cats and nociceptive electrical stimulation of the hind limb in the intact rabbit were the same. Doses of the drugs for which weakening of impulse summation was observed during direct stimulation of the thalamic nuclei are given below (in mg/kg): chlordiazepoxide 1-2, diazepam 0.1-0.2, imipramine 0.1, and morphine 0.5.

During direct stimulation of the thalamic centers in cats impulse summation is thus not facilitated by chlordiazepoxide, diazepam, imipramine, or morphine. Weakening of impulse summation in the thalamic centers is produced by chlordiazepoxide, diazepam, and imipramine in doses which produce facilitation of impulse summation in the intact central nervous system during nociceptive (electrical) stimulation. These

* At a lower frequency of stimulation summation of impulses could not be detected.

doses are from two to four times smaller than those causing weakening of impulse summation in spinal animals. Presumably the thalamic centers are more sensitive than the spinal centers to chlordiazepoxide, diazepam, imipramine, and morphine. However, it must be remembered that after transection of the spinal cord its sensitivity to pharmacological agents may vary on account of removal of the influence of higher levels of the CNS on its excitability.

It can be concluded from the data given above on the effect of tranquilizers and antidepressants on heteromodal impulse summation at different levels of the CNS that strengthening of impulse summation through the influence of tranquilizers and antidepressants is observed only during nociceptive stimulation of peripheral receptors, and that during stimulation of other modalities (photic or acoustic) this phenomenon is not observed. Consequently, the facilitatory effect of tranquilizers and antidepressants is exhibited only toward impulses of a particular modality. The characteristics distinguishing the action of these substances described above evidently depend on the functional systems through which the effect is produced.

LITERATURE CITED

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2. S. Courvoisier, J. Fournel, R. Ducrot, et al., Arch. Internat. Pharmacodyn., 92, 305 (1953).