INTERACTION BETWEEN EFFECTS OF LYSERGIC ACID DIETHYLAMIDE AND CHLORPROMAZINE AT THE SINGLE NEURON LEVEL IN THE MESENCEPHALIC RETICULAR FORMATION

T. T. Bondarenko

UDC 615.214.015.4:612.823.5

The same neurons of the mesencephalic reticular formation can respond both to lysergic acid diethylamide (LSD) and to chlorpromazine. Complex interaction between the effects of LSD and chlorpromazine evidently takes place at the level of these neurons. Chlorpromazine acts on both inhibitory and facilitatory effects of LSD, and its action may be either antagonistic or synergic. It is concluded that an adrenergic component is present in the mechanism of action of LSD on the CNS.

There is considerable experimental evidence to show that the psychotomimetic effect of lysergic acid diethylamide (LSD) is connected with its action on certain neuromediator and enzyme systems of the brain [7, 16-19]. However, the experimental data on the neurochemical nature of the action of LSD on the CNS are contradictory. Some workers consider that LSD affects serotoninergic brain structures, and that the effects of LSD and serotonin may be either antagonistic or synergic [13, 15]. Other workers consider that a leading role in the mechanism of action of LSD is played by adrenergic brain structures [2, 11], especially the adrenergic structures of the mesencephalic reticular formation (RF) [2].

Few investigations of this subject have been conducted at the single-unit level. For instance, an investigation of neurons of the mesencephalic RF by means of microiontophoresis has shown that LSD behaves antagonistically toward the excitatory effect of serotonin but has no action on its inhibitory effect or on the excitatory effect of noradrenalin [8]. The writer showed previously [3] that LSD acts directly on neurons of the hippocampus and mesencephalic RF.

The object of the present investigation was to study the neurochemical nature of the action of LSD on the neurons of the mesencephalic RF and the role of adrenergic structures in this process. The drug used to act on the adrenergic brain structures was chlorpromazine, which has a blocking effect on them.

EXPERIMENTAL

Male albino rats weighing 200-300 g were anesthetized with urethane (1.3-1.4 g/kg) for the acute experiments. The technique of extracellular recording of unit activity was described previously [3].

After the spontaneous unit activity had been recorded the animal was injected subcutaneously with LSD in a dose of 0.5 mg/kg. Unitary responses to LSD were recorded, after which the rat was given an intravenous injection of chlorpromazine (15-30 mg/kg), and unit activity was again recorded for 30-40 min.

The activity of 24 mesencephalic RF neurons was studied.

Laboratory of Psychopharmacology, Professor V. P. Serbskii Central Research Institute of Forensic Psychiatry, Ministry of Health of the USSR, Moscow. (Presented by Academician P. K. Anokhin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 74, No. 11, pp. 44-47, November, 1972. Original article submitted December 29, 1971.

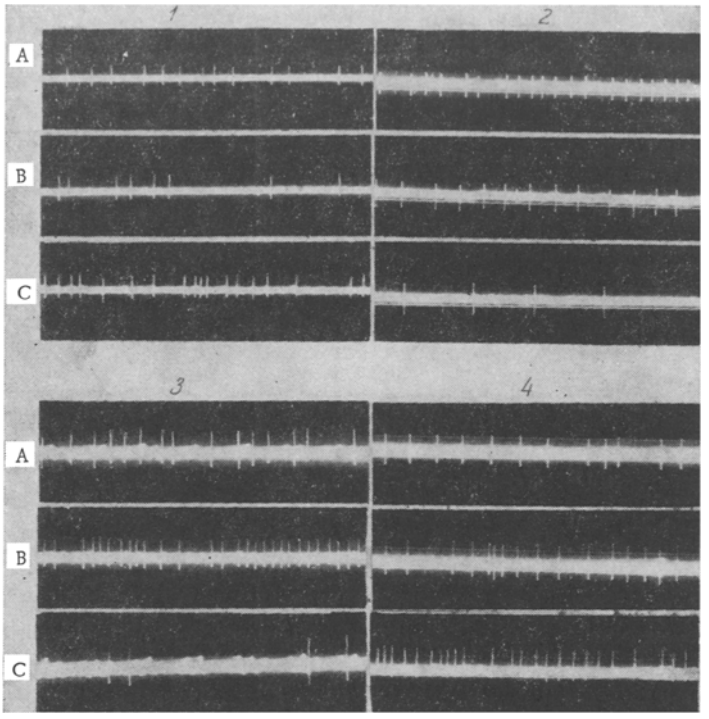

Fig. 1. Types of interaction between effects of LSD and chlorpromazine at the single unit level in the mesencephalic RF: A) spontaneous unit activity; B,C) change in unit activity under the influence of LSD and chlorpromazine, respectively. 1-4) Types of interaction (explanation in text).

EXPERIMENTAL RESULTS

Of the 24 mesencephalic RF neurons studied, 22 responded to LSD and 21 to chlorpromazine; 19 neurons responded to both drugs. Four types of interaction between the effects of LSD and chlorpromazine at the neuronal level were identified (Fig. 1): type 1) LSD inhibits unit activity and chlorpromazine facilitates it (7 neurons); type 2) LSD inhibits unit activity while chlorpromazine inhibits if further still (3 neurons); type 3) LSD facilitates unit activity and chlorpromazine inhibits it (5 neurons); type 4) LSD facilitates unit activity and chlorpromazine potentiates this facilitation (4 neurons).

Antagonism between the effects of LSD and chlorpromazine (types 1 and 3 of interaction) was thus observed rather more often (in 12 of 19 cases) than synergism (types 2 and 4 of interaction). Antagonistic relations are evidently more typical for these drugs.

When different doses of chlorpromazine were used, antagonism and synergism between the effects of LSD and chlorpromazine were exhibited with unequal frequency. When chlorpromazine in a dose of 15 mg/kg was given after LSD (5 experiments, for instance, antagonism was observed in 2 cases and synergism in 3). If the dose of chlorpromazine was 30 mg/kg (9 experiments), antagonism was observed in 7 cases and synergism in 2. Consequently, with a larger dose of chlorpromazine its action was antagonistic to that of LSD much more often than if a smaller dose were given.

These results show that the same mesencephalic RF neurons can respond to both LSD and chlorpromazine. The changes in RF unit activity observed under the influences of these drugs evidently indicate that complex interaction between the effects of LSD and chlorpromazine take place at the level of these neurons. The possibility cannot be ruled out that in some cases these two drugs did not act directly on the neuron studied, but indirectly through other neurons from which the test neuron receives impulses. If, however, the test neuron can receive impulses from other neurons, it must form a single and neurochemically specific system with these neurons. It can be concluded from results showing that chlorpromazine acts mainly on adrenergic brain substrates [1, 10] that the RF neurons on which interaction between the effects of LSD and chlorpromazine was observed belong to the group of adrenergic brain structures. Consequently,

the microelectrode investigation confirms the presence of an adrenergic component in the mechanism of action of LSD, in agreement with results obtained by other workers [2, 11].

The varied character of interaction between the effects of LSD and chlorpromazine at the single unit level in the mesencephalic RF must also be emphasized. For instance, chlorpromazine may act on both the inhibitory and the facilitatory effects of LSD, and with respect to both these effects it may be either antagonistic or synergic.

Several writers have described antagonism between LSD and chlorpromazine in their influence on the CNS [2, 12]. This antagonism could be deduced from the comparison of certain results. For instance, it has been shown by a microelectrode method that LSD does not abolish the excitatory effect of noradrenalin [8], whereas chlorpromazine inhibits this effect [9]. Consequently, LSD and chlorpromazine may behave in diametrically opposite ways toward adrenergic brain neurons; this may play a role in their antagonism.

Only one investigation has shown the presence of synergism in the action of LSD and chlorpromazine on the CNS [14]. This worker has shown that the preliminary injection of small doses of chlorpromazine (0.15 mg/kg) prevents the action of LSD on behavior (antagonism). Large doses of chlorpromazine (1 mg/kg), on the other hand, potentiate the effect of LSD (synergism). In the present experiments, both antagonistic and synergic relationships were observed between the effect of chlorpromazine and the action of LSD on RF unit activity, regardless of the dose of chlorpromazine. With the larger dose, antagonism between the effects of these drugs was seen more often than synergism.

The character of the interaction between the effects of LSD and chlorpromazine is apparently determined more by qualitative differences between the neurons on which this interaction takes place than by the quantitative ratio between these drugs in the body. There is evidence in the literature of the neurochemical heterogeneity of the mesencephalic RF [4] and of the possible action of chlorpromazine not only on adrenergic, but also on cholinergic and serotoninergic brain structures, although to a lesser degree [5, 6]. The existence of different types of interaction between the effects of LSD and chlorpromazine at the single unit level is evidently due to the fact that this interaction can take place on RF neurons which differ in their neurochemical behavior.

LITERATURE CITED

1. P. K. Anokhin, Fiziol. Zh. SSSR, No. 11, 1072 (1957).
2. I. P. Anokhina, Fiziol. Zh. SSSR, No. 9, 1016 (1967).
3. T. T. Bondarenko, Byull. Éksperim. Biol. i Med., No. 10, 53 (1971).
4. R. Yu. Il'yuchenok and M. D. Mashkovskii, Fiziol. Zh. SSSR, No. 11, 1352 (1961).
5. I. V. Markova, Byull. Éksperim. Biol. i Med., No. 7, 49 (1962).
6. E. Stoika, Zh. Vyssh. Nervn. Deyat., No. 5, 888 (1962).
7. I. P. Anokhina, T. T. Bondarenko, and N. A. Khristolubova, Proceedings of the 25th International Congress of Physiological Science, Vol. 9, No. 50, Munich (1971), p. 21.
8. R. J. Boakes, P. B. Bradley, I. Briggs, et al., Brain Res., 15, No. 2, 529 (1969).
9. P. B. Bradley, J. H. Wolstencroft, L. Hosli, et al., Nature, 212, 1425 (1966).
10. P. Dell, M. Bonvallet, and A. Hugelin, Electroenceph. Clin. Neurophysiol., 6, 599 (1954).
11. A. K. Dixon, Experientia, 24, 743 (1968).
12. B. Djahanguiti and N. Guiti, Nature, 212, 87 (1966).
13. D. X. Freedman, Lloydia, 29, 303 (1966).
14. M. F. Halasz, J. Formanek, and A. S. Marrazzi, Science, 164, 569 (1969).
15. N. Kawai and C. Yamamoto, Brain Res., 7, 325 (1968).
16. B. E. Leonard and S. R. Tonge, Life Sci., 8, 815 (1969).
17. R. Pavlin, J. Neurochem., 10, 195 (1963).
18. J. A. Rosecrans, R. Lovell, and D. X. Freedman, Biochem. Pharmacol., 16, 2011 (1967).
19. T. Shanthaveerappa, K. Nandy, and G. Bourne, Acta Neuropath. (Berlin), 3, 29 (1963).