BLOCKADE BY BROM-LYSERGIC-ACID-DIETHYLAMIDE (BOL) OF THE POTENTIATING ACTION OF SEROTONIN AND RESERPINE ON HEXOBARBITAL HYPNOSIS

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Intraperitoneal injection of serotonin potentiates the hypnotic effect of hexobarbital in mice (Shore, Silver and Brodie, 1955). This potentiation is blocked by lysergic-acid-diethylamide (LSD), a compound that blocks the action of serotonin on smooth muscles (Gaddum, 1953) and induces a schizophrenic-like state in man (Stoll and Hofmann, 1943).

Reserpine increases urinary excretion of 5-hydroxy-indole-acetic acid (Shore, Silver and Brodie, 1955a), a major metabolite of serotonin, and releases serotonin from the intestine (Pletscher, Shore and Brodie, 1955). Like serotonin, reserpine potentiates the hypnotic effect of hexobarbital in mice (Brodie, Shore, Silver and Pulver, 1955); this potentiation is blocked by LSD. Thus the suggestion has been made that certain actions of reserpine may be mediated through the liberation of serotonin.

2-Brom-d-lysergic-acid-diethylamide (BOL)[2] is a lysergic acid derivative and, like LSD, inhibits the action of serotonin on rat's uterus (Sollero, Page and Salmoiraghi, 1956). The pharmacological actions of the two structurally similar compounds are, however, not identical. While LSD fails to block the action of serotonin on guinea pig ileum (Gaddum and Hameed, 1954), BOL proved very effective (Sollero, Page and Salmoiraghi, 1956). Furthermore, BOL, in contrast to LSD, does not seem to induce mental or psychic disturbances in man (Cerletti and Rothlin, 1955).

In view of these different pharmacological activities of LSD and BOL it seemed important to determine if BOL, like LSD, could inhibit the potentiation of the hypnotic effect of hexobarbital produced by serotonin and reserpine.

METHODS. Unfasted adult male mice from 15 to 25 grams and female rats from 190 to 290 grams were used only once.

"Sleeping time" was measured as the time interval between loss and return of righting reflex following intraperitoneal injection of hexobarbital sodium (Evipal).

BOL (10 mgm./kgm.) was given in a single dose 1 hour before hexobarbital (100 mgm./kgm. in mice; 150 mgm./kgm. in rats). Serotonin (20 mgm./kgm. as serotonin creatinine sulphate) was injected 10 minutes before the hypnotic; reserpine (Serpasil—5 mgm./kgm.) 1 hour before the hypnotic. All drugs were injected intraperitoneally.

Significance of differences in sleeping time was calculated by dividing the differences

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TABLE 1

Duration of hypnosis in mice and rats

	Hexobarbital Alone	BOL + Hexobarbital	Serotonin + Hexobarbital	BOL + Serotonin + Hexobarbital	Reserpine + Hexobarbital	BOL + Reserpine + Hexobarbital
	min.	*min.*	*min.*	*min.*	*min.*	*min.*
Mice	19.4 ± 1.2 (14)	14.8 ± 2.2 (11)	40.3 ± 3.4 (11)	18.2 ± 3.3 (12) [4.6]	33.6 ± 2.9 (11)	17.0 ± 1.2 (12) [5.3]
Rats	59.3 ± 1.8 (9)	60.7 ± 1.9 (7)	95.4 ± 4.8 (8)	57.3 ± 1.5 (11) [7.4]	90.0 ± 5.0 (9)	71.4 ± 3.2 (12) [3.3]

Values for duration of hypnosis are means ± standard error of the mean.
Numerals in parentheses indicate the number of animals in each series.
Numerals in squared brackets refer to significance ratios, calculated by the formula: $\frac{M_1 - M_2}{\sqrt{SE_{M1}^2 + SE_{M2}^2}}$. These ratios indicate that the differences between means are significant at a probability level of <0.01.

between means by the standard error of difference of the means, accepting a ratio of 3 or more as significant.

RESULTS. Results are summarized in table 1.

Intraperitoneal injection of BOL (10 mgm./kgm.) in normal mice and rats decreased their spontaneous activity as compared, by continuous observation, with control animals, but BOL did not prolong the hypnotic effect of hexobarbital.

Injection of either serotonin or reserpine also caused a decrease of spontaneous activity in normal mice and rats. Both these drugs significantly prolonged the duration of the hypnotic effect of hexobarbital.

When mice and rats were pretreated with BOL, the potentiation by serotonin or reserpine of the hypnotic effect of hexobarbital was inhibited.

DISCUSSION. Brodie, Shore, Silver and Pulver (1955) and Shore, Silver and Brodie (1955) have found that potentiation of the hypnotic effects of hexobarbital by serotonin and reserpine is not dependent upon a change of the rate of bio-transformation of the barbiturate or from an altered uptake of the hypnotic from the brain; instead, serotonin and reserpine presumably act by increasing the sensitivity of the central nervous system to the hypnotic.

BOL effectively antagonizes this potentiation, behaving like LSD. Thus, introduction of a bromine group into the molecule of lysergic-acid-diethylamide (LSD) enhances the serotonin-blocking activity of the compound on smooth muscles (Sollero, Page and Salmoiraghi, 1956) and does not alter its antagonism to serotonin in the central nervous system. Yet BOL is said to be ineffective, in contrast to LSD, in producing mental changes in man (Cerletti and Rothlin, 1955). If LSD produces a schizophrenic-like state by blocking the action of the normally occurring serotonin in brain, it is difficult to understand why BOL does not produce this effect.

SUMMARY

1. 2-Brom-d-lysergic-acid-diethylamide (BOL) produces a decrease of spontaneous activity in normal mice and rats and does not prolong the hypnotic action of hexobarbital.

2. The hypnotic effect of hexobarbital is prolonged by serotonin and reserpine and this action is blocked by injection of BOL.

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