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BRIEF COMMUNICATION

Biphasic Dose-response Effects of N-N-Dimethyltryptamine on the Rat Startle Reflex[1]

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DAVIS, M. AND M. H. SHEARD. *Biphasic dose-response effects of N-N-dimethyltryptamine on the rat startle reflex.* PHARMAC. BIOCHEM. BEHAV.**2**(6) 827–829, 1974.– The startle reflex was measured in 4 groups of 10 rats each after intraperitoneal injection of saline or 0.12, 0.25, 0.50 or 4.00 mg/kg N-N-dimethyltryptamine (DMT). Low doses (0.25 and 0.50) of DMT augmented startle but the high dose (4.0) depressed startle. This biphasic dose-response relationship is consistent with the hypothesis that startle is enhanced when midbrain raphe neurons are inhibited but depressed when cells post-synaptic to raphe neurons are also inhibited.

DMT N-N-dimethyltryptamine Startle

RECENT evidence suggests that the midbrain raphe neurons serve an important role in the modulation of the acoustic startle reflex. Lesions of these nuclei result in a profound increase in the amplitude of the startle reflex [3]. Very low doses of lysergic acid diethylamide (LSD), which inhibit raphe neurons [1] augment startle [4]. With high enough doses, however, LSD appears to suppress startle somewhat [4]. Microiontophoretic studies, in which LSD has been applied directly to raphe neurons and neurons which are postsynaptic to the raphe, indicate that low doses of LSD specifically and directly inhibit the firing rate of raphe neurons [5]. With high enough doses, however, LSD also inhibits cells which are postsynaptic to the raphe [5]. Based on these results it has been suggested that startle amplitude is enhanced when raphe neurons are inhibited but is depressed when cells postsynaptic to the raphe nuclei are also inhibited [4].

Another hallucinogenic drug that has similar effects on the raphe neuronal system is N-N-dimethyltryptamine (DMT). Low doses of DMT applied microiontophoretically inhibit the firing rate of raphe neurons whereas high doses also inhibit cells postsynaptic to the raphe nuclei (Haigler and Aghajanian, in preparation). In a previous study, doses of 1 to 16 mg/kg of DMT depressed startle, with a greater depression the higher the dose [2]. Doses lower than 1.0 mg/kg were not used. Given the fact that low doses of DMT can directly and specifically inhibit unit firing in raphe neurons without a detectable effect on cells that are postsynaptic to the raphe, low doses of DMT should also augment startle, if inhibition of the raphe nuclei is indeed associated with an enhancement of startle. If, therefore, a sufficiently wide range of doses were employed, startle amplitude should bear a biphasic relationship to DMT: enhancement at low doses and depression at high doses. The purpose of the present study was to test this possibility.

METHOD

Animals

Forty naive, male, albino Sprague-Dawley rats that weighed between 250–300 g were used. Prior to testing the rats were housed in group cages of 4–5 rats each in a large colony room that was maintained on a 12 : 12 light–dark schedule. Food and water were continuously available.

Apparatus

The apparatus has been described in detail elsewhere [3]. Briefly, 5 separate stabilimeter devices were used to record the amplitude of the startle response. Each stabili-

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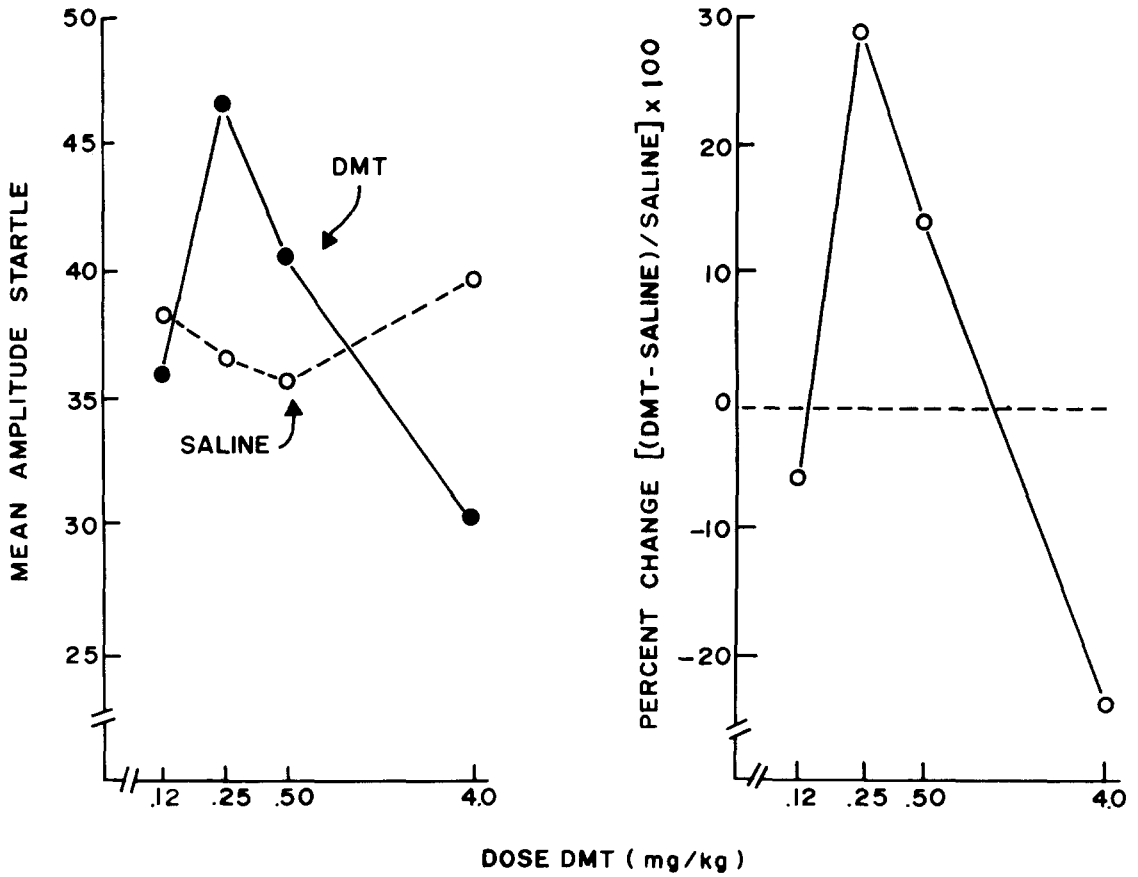

FIG. 1. Left: Mean amplitude startle response after saline or various doses of DMT. Right: Same data expressed as percent change in startle after DMT relative to saline.

meter consisted of a 3.5 x 6 x 6 in. Plexiglas and wire mesh cage suspended between compression springs within a wooden frame. Cage movement resulted in displacement of an accelerometer where the resultant voltage was proportional to the velocity of displacement which defined the amplitude of the startle response. The stabilimeters were housed in a dark, ventilated, sound attenuated chamber 45 in. from a loudspeaker. The startle stimulus was a 4000 Hz, 90 msec tone having a rise-decay time of 5 msec. Background white noise, provided by a white noise generator, was 46 dB as measured on the A-scale of a General Radio Model 1551-C sound level meter.

Procedure

On the first experimental day each rat was placed in a stabilimeter and after 5 min presented with 10, 115-dB tones at a 30 sec interstimulus interval. Based on the average startle amplitude across these 10 tones, the 40 rats were divided into 4 groups of 10 rats each, with each group having similar means and variances.

On the second experimental day which came 24 hr later, half the rats in each group were injected intraperitoneally with 1 cc 0.9% saline and the other half with either 0.12, 0.25, 0.50 or 4.0 mg/kg DMT, using a different matched group for each of the 4 doses. Immediately after the injections the rats were placed in the chamber and 5 min later presented with a series of 30 tones, with 10 tones at each of 3 intensities (110, 115, and 120 dB). The various intensities were presented at a 30 sec interstimulus interval in an irregular order such that each intensity followed itself and every other intensity equally often and the various intensities were distributed uniformly over the entire sequence of 30 tones. This multiple intensity test procedure was used to insure that startle amplitude would be sampled over a wide range of the scale, since startle amplitude shows a strong dependence on the intensity of the acoustic stimulus.

On the third experimental day (24 hr later) the identical procedure was conducted except in this case drug conditions were reversed so that animals that received saline the day before now received DMT and vice-versa. In this way each animal served as his own control with respect to drug condition while dosage was varied between animals.

RESULTS

The left panel in Fig. 1 shows the mean amplitude startle response following injection of saline or DMT at each of the 4 doses that were used. The right panel shows the percent DMT-saline difference at each of the 4 doses. The results were collapsed over days and over the 3 test intensities since the pattern of differences was highly similar on each day and at each of the 3 test intensities. Figure 1 indicates that over this dose range, DMT did have a biphasic effect on startle amplitude which was highly significant, $F(1,36) = 17.29$, $p<0.001$. A dose of 0.25 mg/kg DMT significantly

augmented startle ($t = 3.11$, $df = 9$, $p < 0.01$) whereas a dose of 4.0 mg/kg significantly depressed startle ($t = 3.55$, $df = 9$, $p = < 0.01$).

A subsequent experiment was also conducted in which rats were injected with saline or 0.5 mg/kg DMT or 4.0 mg/kg DMT (n = 20 for each condition) and then presented with tones for 40 min at a 10 sec ISI immediately after being injected to evaluate the time course of the DMT effects. With 0.50 mg/kg dose, startle was potentiated very rapidly with the peak effect occurring in about 4 min and no potentiation beyond 12 min. With the 4.0 mg/kg dose, startle was depressed after about 5 min with peak depression at 10 min with no depression beyond 20 min.

DISCUSSION

The present results confirm the expectation that low doses of DMT should enhance startle similar to low doses of LSD. They also replicate the previous finding that high doses of DMT depress startle. Although it is possible that peripheral effects of DMT or the effects of DMT on brain sites other than the raphe nuclei may have influenced startle in a biphasic way, the data are at least compatible with the idea that inhibition of the midbrain raphe nuclei is associated with an enhancement of startle while inhibition of cells postsynaptic to the raphe is associated with a depression of startle.

It should be pointed out that the magnitude of startle potentiation by low doses of DMT was small and somewhat less than potentiation by low doses of LSD. For example, under similar conditions, LSD caused a 50–70% increase in startle [4] compared to the 15–30% increase in the present study using DMT. On the other hand, depression of startle with high doses of DMT seems to be easier to produce than depression of startle with high doses of LSD. Put another way, the ratio between doses that augment startle and ones that depress startle seems to be bigger with LSD than with DMT. While a specific study which directly compared different doses of DMT and LSD on startle would be necessary to demonatrate this difference, this impression is consistent with very recent evidence which indicates DMT to be more potent than LSD in depressing cells postsynaptic to the raphe at doses which have equivalent effects on raphe neurons themselves (Haigler and Aghajanian, in preparation).

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