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Pimozide-induced Extinction in Rats: Stimulus Control of Responding Rules Out Motor Deficit[1]

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FRANKLIN, K. B. J. AND S. N. McCOY. *Pimozide-induced extinction in rats: Stimulus control of responding rules out motor deficit.* PHARMAC. BIOCHEM. BEHAV. 11(1) 71–75, 1979.—Rats stopped responding for electrical stimulation of the brain following pretreatment with the dopamine antagonist pimozide, as well as following truncation of brain stimulation trains. In either case the extinguished responding was temporarily reinstated on presentation of a light if the light had previously signalled reward but not if the light had had no such significance. These results indicate that pimozide reduces self-stimulation by abolishing the rewarding effect of brain stimulation rather than by interfering with motor ability.

Self-stimulation Reward Reinforcement Dopamine Pimozide Neuroleptics Akinesia

RECENT neurochemical studies of electrical self-stimulation of the brain (ICS) indicate that ICS is critically dependent on brain dopamine (DA [3,4]) but there is controversy as to whether DA is important for the rewarding effect of brain stimulation per se, or only for the motor abilities required by the ICS response [9].

Evidence suggesting that DA might be involved in the rewarding or motivation-inducing effect of brain stimulation is that ICS sites were found along the course of DA pathways in the brain [6,23] and that ICS is especially sensitive to the effects of dopaminergic drugs [26,31]. A defining characteristic of rewards is that responses followed by rewards are increased or maintained in frequency while responses that are unrelated to the occurrence of rewards tend to decrease in frequency [16,29]. Brain stimulation is believed to be rewarding precisely because it acts in this manner. Analogously, if DA release were important to the occurrence of reward we would expect the relationship of DA release to a response to be critical. Thus, drugs which increase the nerve impulse-dependent release of DA [30] markedly facilitate ICS [5, 13, 17] while drugs which have tonic DA activity independent of the nerve impulse may interfere with ICS [13, 17, 19], presumably because the contingency between the response and the release of DA by brain stimulation is preserved in the former, but not the latter, case [1, 5, 13, 17]. As might be expected, both types of DA stimulant act as rewards to increase the frequency of responding when they are presented as a consequence of the response [2,22]. Conversely, responding eventually ceases (extinction) when the response-reward contingency is discontinued whether the reward be food or water, brain stimulation [21] or a DA-stimulant [22]. Likewise, blocking brain DA activity depresses or abolishes ICS [3, 4, 27, 31] as would be expected if the rewarding quality of ICS is reduced by DA block. However, in this case the decrement in ESB might also arise from non-motivational effects of blocking DA. It is well known that loss of brain DA activity causes Parkinsonian-like akinesia [18] and this motor disorder, rather than reduced reward, may be responsible for the loss of ESB following DA blockade [10,27]. On this interpretation the facilitatory effects of indirect DA stimulants are the results of their arousing and locomotor-stimulant [24] actions while the disruption of ICS by direct DA stimulants could be a consequence of stereotyped abnormal motor activity which can be readily observed with moderate doses of these drugs [8].

One line of evidence cited in favour of a motivational role for DA is that the decline in ICS produced by DA blockade closely resembles extinction of ICS when the rewarding current is turned off, i.e. an animal pretreated with a DA antagonist (pimozide or butaclamol) responds at a normal rate at the beginning of the ICS session and slows after a few minutes [11]. However, this pattern of responding does not preclude a motor deficit. It is conceivable that a deficit is not manifest until the response has been performed several times—the animal might be excessively fatiguable, for example—and in this regard it has been noted that rats with akinesia-producing lesions of the nigro-striatal DA system may begin to feed, locomote or investigate a stimulus but soon cease [14,20].

It was reasoned that if DA antagonists depress ICS by interfering with the animal's ability to respond, ICS, once blocked, should not recommence till the animal recovers from the drug or from the previous bout of activity. Alternatively, if DA antagonists reduce the rewarding effect of brain

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stimulation it should be possible to reinstate responding by presenting the animal with a discriminative stimulus which has previously signified the availability of reward.

METHOD

Animals

Animals were 18 adult male hooded rats which self-stimulated through "monopolar" stainless steel electrodes (Plastic Products, Roanoke VA) implanted in the lateral hypothalamus. Electrodes were implanted under Nembutal anaesthesia (60 mg/kg) aimed at a point 0.5 mm behind bregma, 1.6 mm lateral to the midline and 8.8 mm below the skull surface. The nose bar was set 5 mm above the inter-aural line.

Apparatus

Rats were trained and tested in a conventional Skinner Box with a response lever at one end set at 7 cm above the floor. The interior of the box was illuminated by a 15 W house light or, in addition, by 2 bright flashing lights (0.5 Hz). The lights were No. 1820, 28 V bulbs set into the box wall 4.5 cm either side of the lever. The sequence of events in the box was automatically controlled.

Drugs

Pimozide (0.25 mg: Janssen) was dissolved in 1 ml 3% Tartaric acid. A 0.25 mg/kg dose was chosen because in pilot studies it was the lowest dose that severely depressed ICS. Pimozide or its acid vehicle were injected IP 4 hr before testing.

PROCEDURE

Training

Animals were first trained to lever press for continuously available 0.64 sec trains of brain stimulation using standard shaping techniques. The minimum current required to maintain lever pressing for 0.64 sec trains was established and reward trains were increased to 1.28 sec at twice the threshold current in order to maintain responding for intermittent reward.

Animals were divided into two groups, nine rats per group. Both groups were trained to respond on a schedule of intermittent reward in which there were 3 min periods when responding was rewarded at varying intervals averaging 15 sec (VI 15) alternating with 3 min periods when every fourth response was rewarded (FR 4). After five 30-min sessions on this schedule reward trains were reduced to 40 msec for 1 session and responding was extinguished to a criterion of 2 min without a response. Rats were then retrained with the schedule modified so that the 3 min periods of VI 15 or FR 4 were separated by 3 min during which no rewards were delivered. Throughout training the two groups experienced the flashing light in different circumstances. For one group (Signalled group) the flashing light was turned on when FR 4 schedule was instituted and remained on through the subsequent period of non-reward till reward reverted to VI 15. Thus light *onset* was correlated with the recommencement of reward on FR 4 following a period of non-reward and light *offset* was correlated with recommencement of reward on VI 15. The second group (Unsignalled group) experienced the flashing light for an equal proportion of the time (50%) but light onset and offset were random with respect to the availability of reward. Throughout training sessions began with a period of VI 15 as often as with FR 4.

Testing

After 6 sessions of training on this regimen, the power of the flashing light to reinstate ICS was tested twice, once after a period of reduced brain stimulation and once after responding was depressed by pimozide (0.25 mg/kg). Four days rest and 2 daily retraining sessions intervened between the two tests and the order of testing was counterbalanced. The signalled and unsignalled groups were tested identically as follows: 4 hr after an IP injection of pimozide or its vehicle the rat was placed in the apparatus with the flashing light off and brain stimulation available on VI 15. Pimozide treated rats received reward trains of 1.28 sec but for vehicle treated rats brain stimulation was reduced to a sub-threshold train of 40 msec. If a rat failed to respond spontaneously within 2 min it was given two free priming stimulations. Once ICS began responses were recorded until no lever presses were emitted for two consecutive minutes. The flashing light was then turned on, the reward schedule was changed to FR 4, and responding was again recorded till no responses were emitted for 2 consecutive min at which time the flashing light was turned off and reward reverted to VI 15. If a rat did not respond within 2 min it was aroused by shaking the apparatus and allowed at least a further 2 min to respond. The test was terminated when rats went 2 min without making another response.

RESULTS

The results are summarized in Fig. 1. It can be seen from Panels A and C that pimozide or reduced brain stimulation initially produced similar decrements of ICS. Under either treatment 16/18 rats commenced responding spontaneously and the other 2 rats responded when primed, these rats also required priming during training. During the first minute of the test session the mean response rate under pimozide (mean=13.7/min) was not significantly different from the rate under reduced stimulation (mean=12.0). However, under both pimozide and reduced stimulation the initial response rate was lower than that recorded at the beginning of the last training session (mean=20.4: $t=3.25$ and $t=3.40$, respectively, $df=17$, $p<0.005$). During training brain stimulation intensity had been adjusted so that animals responded reliably throughout a 30 min session but on test days 17/18 rats under reduced stimulation, and 14/18 rats under pimozide, had ceased responding within 30 min ($p<0.02$ Sign Test) and all rats reached the extinction criterion within 40 min. The number of responses emitted in extinction was not affected by the type of training but more responses were emitted under pimozide than under reduced stimulation ($F(1,16)=14.32$, $p<0.01$). The curves in Fig. 1A and 1C suggest that rats continued to respond at very low rates for many minutes but this is in part an artifact of averaging. Individual rats took from 3–40 min to reach extinction criterion (mean ± SD=14.5 ± 8.8 min for reduced stimulation: and 20.4 ± 11.1 min for pimozide).

The effect of the flashing light is shown in Panels B and D of Fig. 1. Consider first Panel B which shows that the light was effective as a discriminative stimulus when ICS was extinguished by reducing brain stimulation. When the light was turned on rats in the Signalled group recommenced re-

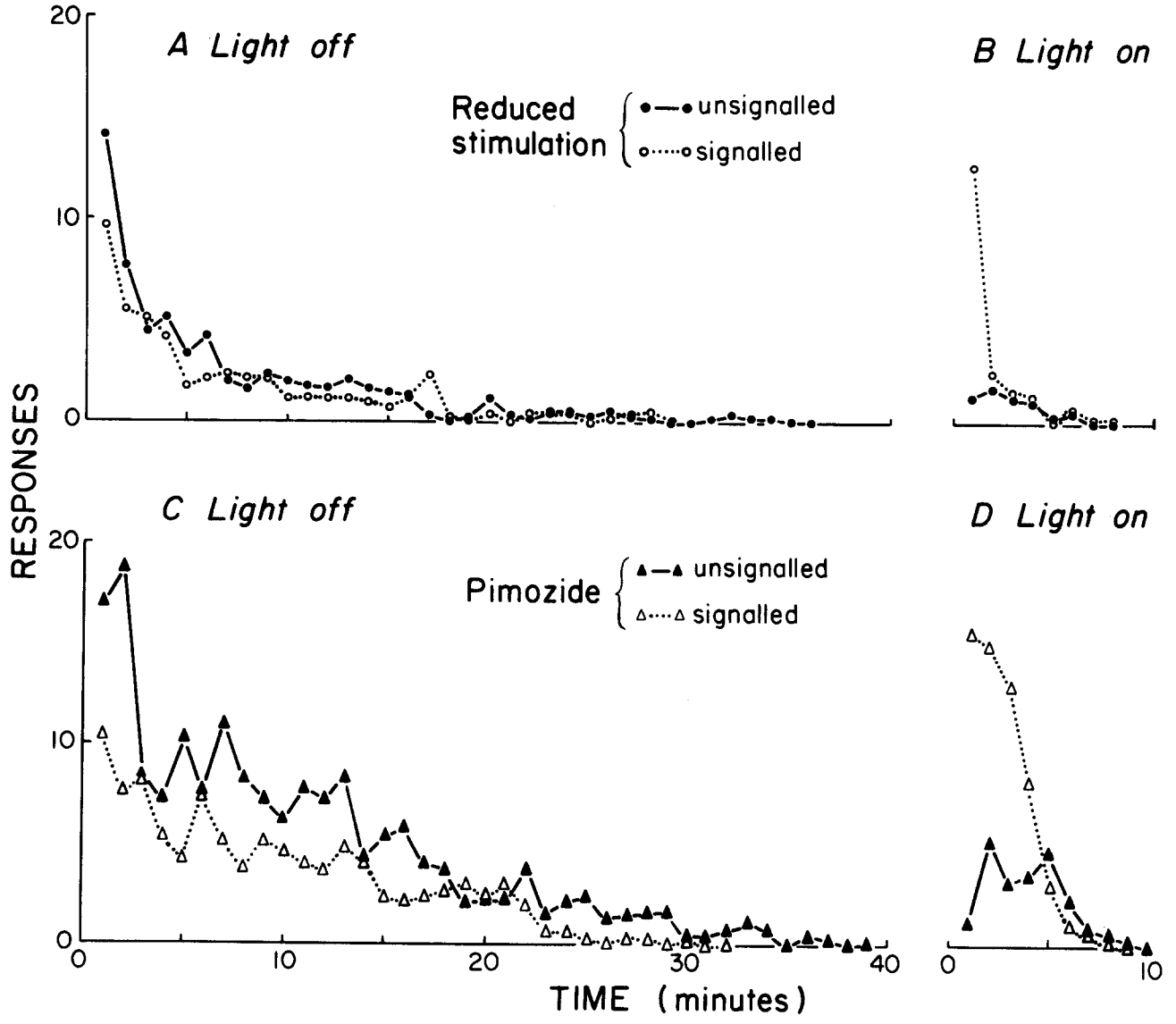

FIG. 1. Mean responses (N=9) emitted per min during initial extinction of ICS in the absence of the flashing light (A and C) and during recovery and subsequent extinction in the presence of the flashing light (B and D). Panels A and B show extinction produced by reducing brain stimulation trains from 128 to 40 msec while Panels C and D show response decrement produced by 0.25 mg/kg pimozide.

sponding with a mean latency of 14.66 sec and at a rate (11.3 responses in the first minute) similar to that recorded in the first minute of the previous extinction period (mean=11.4). In contrast the Unsignalled group made few responses (mean=1.33/min) after long delays (mean latency 78.53 sec). The differences between the Signalled and Unsignalled groups in latency and response rate during the first min were highly significant ($F(1,27)=9.36$: $F(1,96)=8.76$, $p<0.005$).

Considering now Panel D of Fig. 1 it can be seen that when responding was abolished by pimozide the effect of the light stimulus was almost identical to that shown in Panel B. Rats in the Signalled group recommenced ESB with a short latency (12.83 sec) and a rate (15.77 responses first minute) that was as fast as that recorded in the first minute of VI (mean=11.9). The latency and response rate were similar to those recorded in the reduced stimulation condition. In contrast, the Unsignalled group treated with pimozide took a mean of 169.3 sec to respond and a few responses (mean=1.22) were emitted in the first minute. The rate and latency to respond did not differ significantly from those recorded for the Unsignalled group under reduced brain stimulation.

The only difference between the pimozide and reduced stimulation conditions was that pimozide-treated rats again responded more persistently once they began to respond so that there were significant differences between pimozide and reduced stimulation conditions in the second ($F(1,33)=10.1$; $p<0.01$) and third minute of FR 4 ($F(1,33)=8.25$; $p<0.01$).

In the third phase of the test when the schedule was returned to VI and the light turned off, response rates were so low that statistical analysis was not meaningful and no differences between conditions could be discerned. This was

not surprising in view of the prolonged extinction on VI schedule the animals had experienced in the first phase of the test. Six out of 18 rats under pimozide and 10/18 under reduced stimulation did not recommence responding spontaneously. After these rats were aroused by shaking the box the rats emitted a mean of 2.0 responses in the first minute under pimozide compared to 1.5 responses under reduced stimulation.

DISCUSSION

When first placed in the apparatus pimozide treated rats commenced responding in a normal manner and then showed the extinction-like decrements in responding that have been previously reported [11,12]. The only difference in responding was that under pimozide treatment rats emitted more responses than under control conditions. Such a difference might be expected because under pimozide there is a powerful priming effect of 1.28 sec brain stimulation trains which cannot be duplicated in the reduced brain stimulation condition. Such priming is known to delay extinction [7] but it is independent of the rewarding effect of brain stimulation [15] and does not seem to be affected by DA blockade [12]. Indeed in this experiment the rats which usually required priming to commence responding at the start of a session, were successfully primed under pimozide.

Since the flashing light was turned on when ESB was maximally depressed, the fact that pimozide treated rats responded as vigorously after light onset as when they were first placed in the apparatus shows that the pimozide induced depression was not the result of a motor deficit. Rather, the reinstatement of ICS by a discriminative stimulus which previously signalled the availability of reward showed that pimozide mimicked the effect of reducing brain stimulation and implies that pimozide interfered with the rewarding effect of brain stimulation. It is interesting to note that degrading the reinforcing power of the primary reinforcer apparently does not interfere with any secondary reinforcing properties of the discriminative stimulus which has previously signified the availability of reward. This result is reminiscent of the general finding that degrading the reinforcing potency of an unconditioned stimulus attenuates the response to a first order conditioned stimulus but does not reduce the response to a second order conditioned stimulus [25]. It may indicate that there is a fundamental difference between the character of first and second order reinforcers paralleling differences between first and second order conditioning [25]. An alternative interpretation might be that stimulus control does not depend on the discriminative stimulus having (secondary) reinforcing properties that substitute for the missing primary reinforcement.

It might be argued that through its association with reward the light was arousing for the Signalled group and that it was the arousing property of the light which restored ICS not its discriminative property. Such an explanation would be suggested by the temporary ameliorating effect of arousal on patients with Parkinson's disease [28]. Against this possibility the arousal produced by shaking the animals was ineffective in restoring ICS by comparison with the flashing light. In Figs. 1B and 1C, it can be seen that there was a slight recovery produced by the presumably arousing effect of flashing light in the Unsignalled group but this effect was delayed by several minutes and was much smaller than the stimulus control exerted by the light (Signalled group). Moreover, the hypothetical arousing property of the light is rapidly lost (Fig. 1D) in spite of the fact that it is still being paired with the reinforcer that supposedly creates its arousing property. Thus the reinforcer that in the past was sufficient to make the discriminative stimulus arousing is apparently no longer effective.

In sum our results show that at a moderate dose pimozide neither prevents ICS nor interferes with the rat's ability to respond to a stimulus signalling the availability of reward. Rather, the brain stimulation reward itself seems to lose its rewarding quality. Furthermore, since pimozide has similar effects on brain stimulation reward and natural rewards [32] our findings support the hypothesis that a DA mechanism is a component of a common neural substrate for reward.

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