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Effects of small doses of haloperidol on timing behaviour

The depressive effects of drugs of the phenothiazine and butyrophenone group are thought to be connected with the inability to block post-synaptic receptors in the central catecholamine neurons (see Andén, Carlsson & Häggendal 1969). Clinically, small doses of some phenothiazines—especially those with a propylpiperazine side chain—and some butyrophenones, e.g. triperidol, appear to have certain stimulating properties (Di Mascio, Havens & others 1961, Lingjaerde 1966). We have observed, and others have reported (Janssen, 1962; Monti & Hance, 1967) the butyrophenone derivative haloperidol to have some stimulant action in small doses.

Four male Sprague-Dawley rats were food-deprived and kept at 80% of their free-feeding weight (278 $\pm$ 6 g). The rats were trained to press a lever in standard behavioural chambers (Model E3125A, Grason-Stadler) to get food pellets (Noyes, 45 mg) on a DRL-20 schedule (Differential Reinforcement of Low rates), whereby a depression of the lever produced the pellet only if it followed the preceeding lever depression by at least 20 s. Every premature lever press (<20 s after the last response) starts the interval again.

The Inter-Response Times (IRT, interval between successive responses) were divided in 3 s categories: 0–2, 3–5, etc. Presses spaced more than 30 s apart were collected in a last category. Leverpress responses were recorded on digital counters and categorized automatically. For each session a mean IRT was calculated. The distribution was symmetrically cut (below 9–12 and above 27–30) around the optimal reinforced IRT (18–21), to avoid an open interval. A grand mean for the control and the different treatments was calculated and a 98% confidence interval determined for the differences between the means (Scheffé, 1959).

Each rat was exposed to daily sessions for 21–22 consecutive days. Experimental sessions were separated by two control sessions. The complete sessions consisted of 15 min adaptation, immediately followed by 60 min, in which responses were recorded. 15 min before the start of the experimental sessions, animals were injected with haloperidol 0·01, 0·02 or 0·03 mg/kg: each dose was tested twice on each rat. No injections were made before any of the control sessions. Drugs were freshly prepared and injected intraperitoneally in a volume of 2 ml/kg.

The effects of the doses of haloperidol on the behaviour variable used are shown in Table 1. After injection of 0·02 mg/kg of haloperidol the IRT distributions showed a statistically significant ($P < 0·02$) increase in the frequency of short IRTs compared to those in the control distributions. That is, the animals pressed the lever more frequently before the required interval had elapsed. The injections of the other doses of haloperidol, 0·01 and 0·03 mg/kg did not significantly alter the IRT distributions. As assessed by gross observation all the animals displayed a normal behaviour.

Table 1. *The effects of different doses of haloperidol on DRL-20* behaviour.* The IRT (Inter-Response Time)-values are grand means of the total IRT means for each treatment. The lower part of the Table gives a 98% confidence interval for the differences between the control value and each of the three haloperidol doses. The difference between controls and 0·02 mg/kg haloperidol is significantly different from zero.

Treatment		IRT ± s.d.	N	
I	Control	19·9 ± 0·8	61	
II	Haloperidol 0·01 mg/kg ..	19·5 ± 0·7	8	
III	Haloperidol 0·02 mg/kg ..	19·4 ± 0·9	8	
IV	Haloperidol 0·03 mg/kg	19·7 ± 0·7	8	
I–II	0·4 ± 0·5			NS
I–III	0·5 ± 0·5			$P < 0·02$
I–IV	0·2 ± 0·5			NS

* Differential reinforcement of low rates (20s)

Thus haloperidol in a narrow dose interval, <0·03 and >0·01 mg/kg, shortened the IRTs. Amphetamine induces a similar effect on timing behaviour, although more pronounced (Sidman, 1955). Amphetamine is thought to exert its stimulant effect through a release of newly synthesized transmitters (*see* Carlsson, 1970). The postsynaptic receptor blockade induced by haloperidol increases the catecholamine turnover, possibly through a negative feed-back mechanism increasing the physiological release of transmitters onto the receptors (see Andén, Carlsson & others 1969). A possible explanation of the observed stimulant effect seen after haloperidol in a dose of 0·02 mg/kg might lie in an increased physiological release of transmitters, which overcame the blockade of the receptors. When the dose of haloperidol was increased the receptor-blockade dominated. It has also been observed in this laboratory that a dose of 0·1 mg/kg haloperidol disrupts the DRL-20 behaviour.

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