DROPERIDOL INHIBITS CARDIAC VAGAL EFFERENTS IN DOGS

B. NASHAN, K. INOUE AND J. O. ARNDT

SUMMARY

The action of droperidol on cardiac vagal efferents was studied in anaesthetized dogs. Droperidol in cumulative doses (0.125, 0.25 and 0.5 mg kg\(^{-1}\) i.v.) inhibited cardiac vagal discharge, shifted pressure—response curves to lower activities, increased heart rate, and decreased arterial pressure slightly. The effects on vagal discharge and heart rate reached their maxima at 0.25 mg kg\(^{-1}\) as a further increase in the dose had no additional effect. The vagal inhibition and the tachycardia were independent of arterial pressure as indicated by the shift in the pressure—response curves and by the fact that they also occurred when the decrease in arterial pressure was prevented. After pretreatment with atropine, droperidol had no effect on heart rate. Thus, droperidol inhibits central vagal drive independently of arterial pressure. This central vagolytic action seems to be the main cause for the positive chronotropic effect of droperidol.

Although droperidol induces a tachycardia in man and in the experimental animal (Janssen et al., 1963; Morrison, Clarke and Dundee, 1970; Ferrari et al., 1974; Müller, 1977), the mechanism of this response remains a matter of debate. A reflex response to the concomitant decrease in arterial pressure via the baroreflexes (Schaper, Jageneau and Bogaard, 1963) or an atropine-like action at the cardiac pace-maker (Parmentier and Dagnelie, 1979) have been suggested as the most likely mechanisms. However, little attention has been paid to the fact that centrally acting drugs, such as droperidol, may affect heart rate by modulating efferent parasympathetic or sympathetic tone, or both. Since, under physiological conditions, heart rate is predominantly under vagal rather than sympathetic control (Bishop, Peterson and Horwitz, 1979) it seemed worthwhile studying the effects of droperidol on those cardiac vagal efferents which constitute the final common pathway to the heart, and the spike activity of which is the neurophysiological correlate of vagal tone to the heart.

MATERIALS AND METHODS

Experiments were performed on 14 mongrel dogs of either sex, weighing 8–18 kg (mean 14 kg). The animals, premedicated with morphine 1 mg kg\(^{-1}\) i.m., were anaesthetized by injecting a mixture of chloralose 50 mg kg\(^{-1}\) and urethane 500 mg kg\(^{-1}\) i.v.

Following tracheal intubation, the animals were allowed to breathe spontaneously.

Anaesthesia was maintained by intermittent injections of the mixture in one quarter of the initial anaesthetic dose every 1–2 h. The last supplement was given at least 30 min before the actual investigation began. Body temperature was maintained at 37–38°C with a heating lamp.

To record nerve activity, the right cervical vagus was freed from the surrounding tissue and covered with paraffin oil at body temperature. The cut central end of nerve bundles separated from the nerve trunk was divided into filaments under a binocular microscope until recordings were obtained of a single fibre. The spikes were detected with a bipolar platinum–iridium electrode, amplified with a capacitance-coupled amplifier (band-pass 30–35000 Hz; input impedance 22 MΩ) and monitored with a loudspeaker and an oscilloscope (Tektronix type 565). The spikes were shaped to standard pulses (5 V, 0.5 ms duration) with a Schmitt-trigger for reliable triggering of a digital counter which yielded a spike count at 1- or 2.5-s intervals. To calculate the average discharge rate (spikes s\(^{-1}\)) the spike counts were averaged for periods of 30 s. The technical details of the spike processing system have been described previously (Arndt, Morgenstern and Samodelov, 1977). Based on previous studies (Jewett, 1964; Katona et al., 1970), a nerve fibre was considered to be a cardiac vagal efferent (cardioinhibitory fibre) if it showed the following characteristics (fig. 1):

1. activation in association with a brief increase in arterial pressure induced by occlusion of the descending aorta with an inflatable balloon (Fogarty...
FIG. 1. Discharge of a cardioinhibitory vagal efferent in relation to changes in arterial pressure and heart rate, and respiration. Original recording from a dog under chloralose-urethane anaesthesia. Arterial pressure was altered by the occlusion of the descending aorta with a balloon. The vagal discharge rate increased during the increase in arterial pressure while the heart rate decreased concomitantly. The vagal activity was inhibited during inspiration.

32-080-8F) which was advanced from a femoral artery, and
(2) inhibition during inspiration.

For measurement of arterial pressure a catheter, connected to a Statham P37B transducer, was placed in the thoracic aorta proximal to the tip of the balloon probe.

Heart rate was derived from the ECG. Respiratory cycle was monitored by a thermistor device attached to the tracheal tube. All data were recorded on a multichannel pen recorder (Beckmann type RM dynograph recorder) and stored on magnetic tape (Teac R-510 data recorder) for the detailed evaluation of the spike activity.

The effects of droperidol on cardiac vagal efferents, and on arterial pressure and heart rate, were evaluated in two ways:

(1) from the time course following injection of droperidol in cumulative doses (0.125, 0.25, 0.5 mg kg⁻¹ i.v. every 15 min) either independently of arterial pressure (n = 9) or at arterial pressures kept slightly above the preinjection values by inflation of the aortic balloon (n = 5), and
(2) from pressure-response curves determined before (control) and 15 min after each injection of the drug.

The pressure-response curves were derived by relating three different values of arterial pressure to corresponding rates of vagal discharge. To achieve this, the arterial pressure was changed by inflating the aortic balloon for about 30 s and deflating it rapidly.

In additional experiments (eight dogs) the effects of droperidol on heart rate and arterial pressure were studied after complete vagolysis with atropine (initial dose 0.15–0.2 mg kg⁻¹ i.v., additional dose 0.05 mg kg⁻¹ every 15 min).

Data are presented as means ± SEM, and to demonstrate the time course at increased values of arterial pressure, in percent of the preinjection val-
DROPERIDOL AND CARDIAC VAGAL TONE

Fig. 2. Effects of cumulative doses of droperidol on discharge rate of a cardioinhibitory vagal efferent, heart rate and arterial pressure. Original recording from a dog under chloralose-urethane anaesthesia. The discharge rate decreased after injections of droperidol, reaching its minimum at the dose of 0.25 mg kg\(^{-1}\). The heart rate increased concomitantly, reaching its maximum at the same dose. Arterial pressure decreased slightly.

Without exception droperidol inhibited cardioinhibitory vagal discharges and induced a period of tachycardia as shown in the recording of a typical experiment (fig. 2).

Both effects were maximum with droperidol 0.25 mg kg\(^{-1}\); an increase in dose had no further effect. On average, the discharge rate of the cardioinhibitory efferents decreased from 3.7 (control) to reach a minimum of 0.9 spikes s\(^{-1}\) whereas heart rate increased from 151 beat min\(^{-1}\) to 200 beat min\(^{-1}\). There was a slight decrease in arterial pressure from 114 mm Hg to reach a minimal value of 99 mm Hg (fig. 3).

Droperidol had no systematic effect on respiratory rate (table I).

The slopes of the regression lines between vagal discharge rate and heart rate varied considerably between the animals (table II). However, in each individual animal both variables correlated strongly and negatively.

To exclude the droperidol-induced decrease in arterial pressure as a possible cause for a baroreflex-mediated vagal inhibition, the decrease in arterial pressure was prevented by controlled occlusion of the thoracic aorta in additional experiments. Although, in these experiments the values of arterial pressure were slightly greater than the preinjection control values (a factor which would normally enhance cardiac vagal activity and lead to bradycardia), vagal activity decreased by 40–100%, and heart rate increased by 10–60% following the ad-
ministration of droperidol (fig. 4). Therefore, it is the vagal inhibition produced by the direct action of the drug on the central nervous system, rather than a reflex response to arterial hypotension, that elicited

![Graph](image1.png)

**Table 1.** Effects of droperidol on respiratory rate (b.p.m.) (mean SEM). n = 9. n.s. = not significant

<table>
<thead>
<tr>
<th>Control</th>
<th>0.125 mg kg⁻¹</th>
<th>0.25 mg kg⁻¹</th>
<th>0.5 mg kg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 ± 4</td>
<td>23 ± 6</td>
<td>25 ± 7</td>
<td>24 ± 7</td>
</tr>
</tbody>
</table>

![Graph](image2.png)

**Fig. 3.** Time course of vagal discharge rate, heart rate and arterial pressure following injections of droperidol in cumulative doses. Results from dogs under chloralose-urethane anaesthesia (mean ± SEM). Significance between the controls and post-injection values: *x = P < 0.05; xx = P < 0.01. After injections of droperidol, vagal discharge rate decreased markedly accompanied by an increase in heart rate and a decrease in arterial pressure.

![Graph](image3.png)

**Fig. 4.** Vagal discharge rate and heart rate after cumulative doses of droperidol when the hypotensive action of droperidol was counteracted by the balloon occlusion of the descending aorta. Data from five dogs under chloralose-urethane anaesthesia. Percent changes of the preinjection values. In spite of a slight increase in arterial pressure (which generally activates vagal cardioinhibitory fibres), vagal discharge rate decreased and heart rate increased after the injection of droperidol.
TABLE II. Regressions and correlation coefficients (r) between vagal discharge rate (X) (spikes s\(^{-1}\)) and heart rate (Y) (beat min\(^{-1}\)).

Number of pairs = 31 for each animal. \(Y = aX + b\)

<table>
<thead>
<tr>
<th>Number of dog</th>
<th>(a)</th>
<th>(b)</th>
<th>(r)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-34.66</td>
<td>227.70</td>
<td>-0.9640</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>-5.82</td>
<td>198.09</td>
<td>-0.9020</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>-17.20</td>
<td>143.04</td>
<td>-0.9348</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>-9.19</td>
<td>239.35</td>
<td>-0.8736</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>-6.14</td>
<td>228.06</td>
<td>-0.7824</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>-8.14</td>
<td>187.62</td>
<td>-0.9565</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>-22.94</td>
<td>180.29</td>
<td>-0.8792</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8</td>
<td>-4.44</td>
<td>213.27</td>
<td>-0.9554</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9</td>
<td>-23.18</td>
<td>231.91</td>
<td>-0.7504</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

the effects on vagal discharge and heart rate.

This conclusion is supported by the analyses of the pressure—response curves in figure 5. Droperidol displaced the curves to lower activities, that is, vagal discharge rate was lower for any arterial pressure following administration of the drug.

Droperidol had no effect on heart rate in those anaesthetized dogs in which vagal influences were abolished by complete vagolysis with atropine (fig. 6). Therefore, the positive chronotropic effects of droperidol are of vagal, and not of sympathetic, origin.

It is of interest to compare the minimum heart rate in these experiments (223 ± 32 beat min\(^{-1}\)) in the absence of vagal influences with those in figure 2 (200 beat min\(^{-1}\)) with a remaining vagal activity of 0.9 spikes s\(^{-1}\) on average. In the latter experiments, heart rate changed by approximately 50 beat min\(^{-1}\) or by about 20 beat min\(^{-1}\) for a change of vagal discharge by 1 spike s\(^{-1}\). Had vagal activity been completely blocked by droperidol, one would have expected the heart rate to increase to about 220

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**FIG. 5.** Pressure—response curves of cardioinhibitory vagal efferents in the control and after injections of droperidol. Results from dogs under chloralose—urethane anaesthesia (mean ± SEM). Significance between the controls and post-injection values: \(x = P<0.05\); \(xx = P<0.01\); \(xxx = P<0.001\). Droperidol inhibited cardiac vagal tone independently of arterial pressure.

**FIG. 6.** Time courses of arterial pressure and heart rate following injections of droperidol in cumulative doses after pretreatment with atropine. Results from dogs under chloralose—urethane anaesthesia (mean ± SEM). Significance between the controls and postinjection values: \(x = P<0.05\); \(xx = P<0.01\); \(xxx = P<0.001\). Droperidol does not affect heart rate after complete peripheral vagolysis, that is the positive chronotropic effects are of vagal origin.
beat min⁻¹ which, in fact, it did after atropine. This suggests a causative relation between vagal discharge and heart rate under droperidol.

**DISCUSSION**

Droperidol inhibited without exception activity in vagal efferents, which we have reason to believe to be cardioinhibitory (that is, to originate from vagal neurones, the discharge of which constitutes the neurophysiological correlate of cardiac vagal tone as the main determinant of heart rate).

For ease of preparation, and to avoid a thoracotomy, we preferred to isolate the single fibres from the cut central stump of the cervical vagus nerve rather than from cardiac branches within the thorax. The former approach renders the identification of the target organ for vagal neurones more difficult. Nevertheless, the vagal fibres which were studied can be considered with certainty to innervate the heart because fibres with a discharge correlating directly with changes in arterial pressure, and inversely with changes in heart rate, were found also in cardiac branches of the thoracic vagus (Jewett, 1964; Iriuchijima and Kumada, 1964). The documented inverse relationship between discharge rate and heart rate under the action of droperidol (table II) justifies our assumption that the vagal efferents studied do innervate the heart, in spite of the lack of anatomical identification of their pathways to the heart.

From the characteristics of cardiac vagal efferents, a drug-induced decrease in arterial pressure is expected to cause a baroreflex-mediated inhibition of their activity. In the present study, a slight decrease in arterial pressure was always observed after injections of droperidol. However, this arterial hypotension, which results from the α-adrenergic blocking action of droperidol (Muldoon et al., 1977), could be excluded as a causative factor since vagal inhibition occurred even when the arterial pressure was increased artificially above its pre-injection values (fig. 4), and because the pressure-response curves were regularly displaced to lower activities after the injection of droperidol (fig. 5). In addition, drug-induced changes in baroreceptor activity could be excluded as possible causes of baroreflex-mediated effects, since droperidol increased baroreceptor activity which, if anything, would activate and certainly not inhibit cardioinhibitory vagal drive (Schumacher and Arndt, 1978). Finally, in agreement with the literature (Yelnosky, Katz and Dietrich, 1964; Canellas et al., 1966), droperidol had no systematic effect on respiration in the doses used. Therefore, it is unlikely that the observed changes were caused by alterations in ventilation.

Consequently, the neurophysiologically documented vagolytic action of droperidol must be initiated by a direct action of droperidol on the central nervous system. How this is brought about cannot be determined precisely from these experiments. Cardioinhibitory vagal efferents originate from cell bodies in the vagal nuclei in the medulla and they mediate as the final common pathway inputs from various sources (Spyer, 1980). Since droperidol blocks dopaminergic neurones in the central nervous system, and since dopaminergic neurones have been identified in the vagal nuclei (Cooper, Bloom and Roth, 1978), it is certainly tempting to speculate that the neurophysiologically documented vagal inhibition is the consequence of an inhibition of such dopaminergic neurones. Irrespective of this speculation, it has been shown that central vagal cardiac tone is strongly inhibited by droperidol – an effect which is independent of arterial pressure and baroreflex control.

Is, however, the accompanying tachycardia the consequence of this central vagolysis? A sympathetic influence and, in agreement with other workers (Carmeliet et al., 1976; Garcia-Barreto et al., 1976), a direct chronotropic action can hardly play a part because, as shown here, droperidol has no effect on heart rate in atropinized dogs. Complete peripheral vagolysis is also unlikely because pupillary dilatation occurs in unanaesthetized cats only with subtoxic doses of droperidol, but not in the pharmacological dose range (Janssen et al., 1963). The experiments in which droperidol was applied locally on the vagal ganglia and the sinus node through the pericardial space showed the minimal effective intrapericardial concentration that just effects the bradycardia in response to electrostimulation of the vagi nerve in cats to be $2.6 \times 10^{-5}$ mol litre⁻¹, and even at $6.6 \times 10^{-4}$ mol litre⁻¹ blockade has been shown not to be complete (König, 1983). Since, in man, even with comparatively large doses ($0.31$ mg kg⁻¹), peak plasma concentration is only $3.0 \times 10^{-4}$ mol litre⁻¹ (far below the minimal blocking concentration (Schaer and Jenny, 1969)), a peripheral vagolytic action of droperidol can hardly contribute to the tachycardia.

This conclusion is supported also by the correlation between the extent of vagal inhibition in relation to the actual heart rates achieved (fig. 3). Had
central vagolysis been complete, one would have expected the heart rate to increase to 220 beat min−1, which is almost the average heart rate seen after complete vagolysis with atropine (fig. 6). Consequently, it seems to be the inhibitory action of droperidol on cardiac vagal efferents which is the prime factor in its positive chronotropic effects.

Do these observations apply also to man? In unpremedicated man droperidol 0.15 mg kg−1 elicited only a transient increase in heart rate (maximum 15%) which lasted for 10 min (Marty et al., 1982) and was obviously less marked than in the anaesthetized dog. This discrepancy in the magnitude of the change in heart rate between the two species may reflect differences in the effective dose ranges because, other than in our experiments in dogs, the complete dose-effect relationship remains obscure in man.

In conclusion, droperidol is capable of inhibiting central cardiac vagal tone. This effect is of central origin, is independent of arterial pressure and baroreflex function, and is in all likelihood the prime factor in the positive chronotropic action of droperidol.

ACKNOWLEDGEMENT

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REFERENCES


DROPERIDOL INHIBIERT DIE KARDIALEN VAGUSEFFERENZEN BEI HUNDEN

ZUSAMMENFASSUNG

An narkotisierten Hunden wurde die Wirkung von Droperidol auf die kardialen vagalen Efferenzen untersucht. Droperidol in ansteigenden Dosen (0,125, 0,25 und 0,5 mg kg⁻¹) inhibierte die kardiale vagale Entladung, verschob die Druckreaktions-Kurve zu niedrigeren Aktivitäten, steigerte die Herzfrequenz und senkte leicht den arteriellen Blutdruck. Die Wirkung auf die vagale Entladung und die Herzfrequenz lag bei 0,25 mg kg⁻¹ bei ihrem Maximum, ein weiterer Dosisanstieg hatte keinen zusätzlichen Effekt. Die vagale Hemmung und die Tachykardie waren unabhängig vom arteriellen Blutdruck, was aus der Verschiebung der Druck-Reaktionskurve und der Tatsache hervorging, daß sie auch bei Verhinderung des Druckabfalls auftreten. Nach Vorbehandlung mit Atropin hatte Droperidol keinen Einfluß auf die Herzfrequenz. Droperidol hemmt also den zentralen vagalen Antrieb unabhängig vom arteriellen Blutdruck. Diese zentrale vagolytische Aktivität scheint der Hauptgrund für den positivchronotropen Effekt von Droperidol zu sein.

SUMARIO

Se estudió en perros anestesiados la acción del droperidol sobre los eferentes vagales cardiacos. El droperidol en dosis cumulativas (0,125, 0,25 y 0,5 mg kg⁻¹) i.v. inhibió la descarga vagal cardíaca, hizo variar las curvas de respuesta-presión a actividades inferiores, aumentó el ritmo cardíaco e hizo bajar ligeramente la presión arterial. Los efectos sobre la descarga vagal y el ritmo cardíaco alcanzaron su máximo a los 0,25 mg kg⁻¹ y un aumento adicional de la dosis no tuvo ningún efecto adicional. La inhibición vagal y la taquicardia eran independientes de la presión arterial tal como lo indicaba la variación en las curvas de respuesta-presión y el hecho de que ocurrieran también cuando se prevenía el descenso de la presión arterial. Después del pretratamiento con atropina, el droperidol no tuvo ningún efecto sobre el ritmo cardíaco. Entonces, el droperidol inhibe la impulsión vagal central independientemente de la presión arterial. Esta acción vagolítica central parece ser la causa principal del efecto cronotrópico positivo del droperidol.