Termination of digitalis-induced ventricular tachycardias by clonidine involves central α_2 -adrenoceptors in cats

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1 Effects of intravenous (i.v.) and intravertebral arterial (i.a.) administration of the α_2 -adrenoceptor agonist, clonidine (Clon) and its antagonist, yohimbine (Yoh, 0.5 mg kg^{-1} , i.v.; 0.05 mg kg^{-1} , i.a.), on ventricular tachycardia (VT) induced by intravenous acetylstrophanthidin (AS) were studied in cats anaesthetized with intraperitoneal chloralose.

2 AS dose-dependently produced cardiac arrhythmias including complete atrioventricular conduction block ($118 \pm 14 \mu\text{g kg}^{-1}$, i.v.), junctional tachycardia ($128 \pm 20 \mu\text{g kg}^{-1}$, i.v.), multiform ventricular premature beats ($157 \pm 21 \mu\text{g kg}^{-1}$, i.v.) and sustained VT ($220 \pm 23 \mu\text{g kg}^{-1}$, i.v.).

3 Doses of Clon (i.v.) required for termination of VT following i.v. Yoh ($62.9 \pm 5.2 \mu\text{g kg}^{-1}$) or i.a. Yoh ($88.5 \pm 16.3 \mu\text{g kg}^{-1}$) were higher than those for termination of VT without Yoh administration ($28.3 \pm 6.2 \mu\text{g kg}^{-1}$). Doses of Clon (i.a.) required for termination of VT without or with i.a. Yoh administration were 5.8 ± 1.0 or $14.8 \pm 3.7 \mu\text{g kg}^{-1}$, respectively, and they were significantly different.

4 These experiments demonstrate that either i.v. or i.a. Yoh antagonizes the antiarrhythmic effect of Clon on AS-induced VT. Since small doses of Clon administered i.a. act predominantly on the central nervous system, we suggest that its antiarrhythmic effect is likely to be on central α_2 -adrenoceptors in the central nervous system.

Keywords: Arrhythmias; α_2 -adrenoceptor agonist; α_2 -adrenoceptor antagonist; digitalis

Introduction

The central nervous system is considered to be involved in the arrhythmogenic effects of digitalis. Pretreatment of animals with reserpine, β -adrenoceptor blocking agents, α_1 -adrenoceptor antagonists, α_2 -adrenoceptor agonists, anticholinergic agents, ganglionic blocking agents and dopamine receptor agonists have been shown to increase the dose of digitalis required to produce cardiac arrhythmias (Lather *et al.*, 1978; Helke *et al.*, 1979).

Clonidine, an α_2 -adrenoceptor agonist, has been demonstrated to suppress the cardiac arrhythmias induced by digitalis in cats (Gillis & Quest, 1972). The reduction of this suppression after spinal transection suggests that clonidine may produce an antiarrhythmic effect through a central action. Whether the α_2 -receptor in the central nervous system is specifically involved was the subject of the present experiment.

Methods

Experimental preparation

Cats of either sex weighing 1.7–3.8 kg were anaesthetized with chloralose (40 mg kg^{-1}) and urethane (400 mg kg^{-1}), intraperitoneally. All cats were cannulated with endotracheal tubes and artificially ventilated with room air. The end expiratory CO_2 concentration was maintained at 3.5–4.5%. The femoral artery and vein were catheterized for blood pressure monitoring and drug administration, respectively. In some experiments, polyethylene tubes (Intramedic) were inserted into the vertebral artery for intravertebral arterial injection of drugs

(Hou *et al.*, 1988). The blood pressure was monitored with a Gould P 231 D transducer connected with an amplifier. The lead II electrocardiogram (ECG) was monitored by a Gould universal preamplifier and displayed continuously on a Tektronix 922 oscilloscope. Blood pressure and ECG were recorded continuously with a Gould ES-1000 recorder.

Induction of ventricular tachycardia

Acetylstrophanthidin (AS, Sigma Chemical Co.) was dissolved in distilled water to give a concentration of $2.5 \mu\text{g ml}^{-1}$ and administered as a bolus intravenous injection (i.v.) at a dose of $20 \mu\text{g kg}^{-1}$, followed by subsequent infusion of $2.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$ until a sustained ventricular tachycardia (VT) had persisted for 5 min. Thereafter, the VT was maintained for at least 25 min. Sustained VT was considered present if a wide QRS tachycardia with atrioventricular dissociation persisted for more than 1 min.

Drug intervention

When the VT had persisted for 10 min after discontinuation of AS infusion, clonidine hydrochloride (Clon, Yung Shin Pharm, Taiwan) was administered as a bolus i.v. or i.a. injection at a dose of $16 \mu\text{g kg}^{-1}$ or $1.6 \mu\text{g kg}^{-1}$, respectively. Additional doses of Clon ($16 \mu\text{g kg}^{-1}$ for i.v.; $1.6 \mu\text{g kg}^{-1}$ for i.a.) were administered if the VT could not be converted to sinus rhythm or a junctional rhythm within 1 min after administration of Clon. Preliminary tests in five cats showed that VT was converted to sinus rhythm by $8 \mu\text{g kg}^{-1}$ in one animal but was not affected by a dose of $4 \mu\text{g kg}^{-1}$.

Usually, the effectiveness of Clon was demonstrated within 1 min after Clon administration. Yohimbine hydrochloride (Yoh, Sigma Chemical Co.) was administered as a bolus i.v. (0.5 mg kg^{-1}) or an i.a. (0.05 mg kg^{-1}) injection at 5 min after

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Figure 1 Protocol for experimental procedures. (A) Intravenous bolus injection of acetylcholinesterase inhibitor (AChEI) followed by subsequent i.v. infusion of AChEI. (B) VT occurrence. (C) Intravenous AChEI infusion discontinued if VT had persisted for 5 min. (D) Yohimbine (Yoh) administered i.v. or i.a. at 5 min after discontinuation of i.v. AChEI infusion. (E) Clonidine (Clon) administered i.v. or i.a. at 10 min after discontinuation of i.v. AChEI infusion. (F) Additional Clon injection(s) was(were) administered if no effect noted.

discontinuation of the AS infusion. This allowed Yoh to interact with the antiarrhythmic effect of Clon which was given at 10 min after the AS discontinuation.

Experimental protocol

To assess the effects of the α_2 -adrenoceptor agonist and antagonist on AS-induced VT, six experimental groups were used. The experimental protocol is shown in Figure 1.

Group (I). Five cats (controls). VT was induced with i.v. AS as described previously. The duration of VT was observed.

Group (II). Ten cats. The induced VT was treated with i.v. Clon.

Group (III). Four cats. The induced VT was treated with i.a. Clon.

Group (IV). Six cats. Yoh i.v. was given at 5 min after discontinuing AS infusion, and was followed by i.v. Clon 5 min later.

Group (V). Five cats. Yoh i.a. was given at 5 min after discontinuing AS infusion and was followed by i.v. Clon 5 min later.

Group (VI). Five cats. VT was induced with i.v. AS. Yoh i.a. was given at 5 min after discontinuing AS infusion and was followed by i.a. Clon 5 min later.

Data analysis

All values are expressed as means $\pm$ s.e. Differences among multiple groups of data were examined with analysis of variance (ANOVA). Student's *t* test corrected for multiple comparisons was used to analyze differences in means when appropriate. A probability of less than 0.05 between two experimental groups was considered as statistically significant.

Results

Effects of acetylcholinesterase inhibitor on blood pressure and cardiac rhythm

Five cats were used in Group I. Figure 2 shows typical tracings from a cat in this group. The basal mean blood pressure (MBP) of the cat was 137 ± 6 mmHg. A gradual increase in the dose of i.v. AS produced a progressive elevation in MBP. The maximal elevation of MBP (170 ± 7 mmHg, $P < 0.001$) was seen just before the occurrence of atrioventricular block (AV block). Further addition of AS produced no change or a slight decline in MBP until the onset of VT (Figure 2).

After AS was administered, the heart rate decreased slightly at the very beginning. Additional doses of AS produced AV block which was soon followed by a junctional tachycardia.

Figure 2 Typical recordings from a cat in Group I showing the effects of intravenous (i.v.) acetylcholinesterase inhibitor (AS) on the electrocardiogram (ECG) and blood pressure (BP). (a) Control (Con) sinus rhythm with cycle length (CL) 340 ms, PR interval at 70 ms, systolic blood pressure (SBP) 150 mmHg and diastolic blood pressure (DBP) 90 mmHg. (b) First degree atrioventricular (AV) block (PR interval 140 ms) with elevated SBP (180 mmHg) and DBP (130 mmHg) when AS dose increased (accumulated) to $75 \mu\text{g kg}^{-1}$. (c) Complete AV block occurred when AS dose increased to $100 \mu\text{g kg}^{-1}$. Note the reduction in BP and pulse pressure (SBP 160 mmHg, DBP 120 mmHg). (d) Junctional tachycardia (CL 350 ms) occurred when AS dose increased to $150 \mu\text{g kg}^{-1}$. SBP (150 mmHg) and DBP (120 mmHg) appeared similar to (c). (e) Ventricular tachycardia (VT) with a CL of 410 ms occurred when AS dose reached $200 \mu\text{g kg}^{-1}$. Note both SBP and DBP markedly decreased to 95 and 65 mmHg, respectively.

The dose required to produce AV block and junctional tachycardia was $118 \pm 14 \text{ mg kg}^{-1}$ and $128 \pm 20 \text{ mg kg}^{-1}$, respectively. Further administration of AS produced multiform ventricular premature contractions (VPCs, $157 \pm 21 \mu\text{g kg}^{-1}$), and this was finally followed by VT ($220 \pm 23 \mu\text{g kg}^{-1}$). The duration of sustained VT after discontinuing AS was from 25 to 48 min (37 ± 4 min, $n = 5$).

Effects of i.v. clonidine on acetylcholinesterase inhibitor-induced ventricular tachycardia

Ten cats were used in this experiment (Group II). As shown in Figure 3a, first degree AV block and ST sagging appeared when the cumulative AS dose was about $100 \mu\text{g kg}^{-1}$. When AS doses were increased to $175 \mu\text{g kg}^{-1}$ (Figure 3b) and $225 \mu\text{g kg}^{-1}$ (Figure 3c), frequent VPCs with AV Wenckebach block and sustained VT appeared. Figure 3d shows the effect of i.v. bolus Clon $16 \mu\text{g kg}^{-1}$ on the sustained VT. The cycle length of VT increased immediately and sinus rhythm was restored within 1 min after Clon. As shown in Figure 3e, regular sinus rhythm with first degree AV block (PR interval 90 ms) and lowered SBP, DBP (100 vs. 60 mmHg) were observed

Figure 3 Recordings show the effect of intravenous clonidine (Clon) on acetylcholinesterase (AS)-induced ventricular tachycardia (VT) in a cat in Group II. Sustained VT appeared when AS dose increased to $225 \mu\text{g kg}^{-1}$ (c), cycle length of VT increased immediately and sinus rhythm restored within 1 min after Clon (d).

15 min after Clon. In this group, the average dose of i.v. Clon for termination of AS-induced VT was $28.3 \pm 6.2 \mu\text{g kg}^{-1}$ (range 16 to $48 \mu\text{g kg}^{-1}$). In these 10 experiments, restoration of sinus rhythm was seen in 7, and junctional rhythm in the other 3 cats, immediately after VT was terminated. In those with junctional rhythm, sinus rhythm was able to be restored within 15 min. The antiarrhythmic effect of Clon on AS-induced VT was observed for 15 min. There was no recurrence of VT.

Effects of i.a. clonidine on acetylcholinesterase-induced ventricular tachycardia

Four cats were used in this experiment. As shown in Figure 4a, a sustained VT was achieved when the AS dose was up to $250 \mu\text{g kg}^{-1}$. Injection of Clon $1.6 \mu\text{g kg}^{-1}$ i.v., terminated the VT. Fifteen seconds after Clon, the sustained VT was terminated and was replaced by sinus rhythm with AV block (Figure 4b). In this experiment, sinus rhythm with 1:1 AV conduction was restored 10 min later and VT did not recur thereafter within a 15-min observation period. In this group, the average dose of i.a. Clon for terminating the AS-induced VT was $5.8 \pm 1.0 \mu\text{g kg}^{-1}$. This dose was much less than that in Group II (5.8 ± 1.0 vs. $28.3 \pm 6.2 \mu\text{g kg}^{-1}$, $P < 0.01$).

Role of the α_2 -adrenoceptor on the antiarrhythmic effect of clonidine

To assess the role of specific central α_2 -receptors in the antiarrhythmic effect of Clon, Yoh was administered via i.v. or i.a. injection to interact with the antiarrhythmic effect of Clon. As shown in Figure 5a, a sustained VT was established when the AS dose was increased up to $200 \mu\text{g kg}^{-1}$. In the presence of

Figure 4 Recordings show the effect of intravertebral arterial (i.a.) clonidine (Clon) $1.6 \mu\text{g kg}^{-1}$ on acetylcholinesterase (AS)-induced ventricular tachycardia (VT) in a cat in Group III. Sustained VT terminated and replaced by sinus rhythm with AV block (b).

Figure 5 Recordings show the effect of i.v. Clonidine (Clon) on ventricular tachycardia (VT) induced with acetylcholinesterase (AS) $200 \mu\text{g kg}^{-1}$ i.v. Yohimbine (Yoh 0.5 mg kg^{-1} i.v.) administered at 5 min after discontinuation of AS in a cat from Group IV (a). Sustained VT converted to sinus rhythm when Clon dose increased to $64 \mu\text{g kg}^{-1}$ (c).

Yoh (0.5 mg kg^{-1} i.v.), bolus i.v. Clon 16 mg kg^{-1} could not terminate VT, but resulted in occasional junctional beats (Figure 5b). The sustained VT was converted to sinus rhythm when the dose of Clon was increased to $64 \mu\text{g kg}^{-1}$ (Figure 5c). Ventricular arrhythmias never occurred thereafter within the 15 min observation period. In this group, after i.a. Yoh, two cats with VT degenerated rapidly into ventricular fibrillation leading to cardiac arrest within 5 min, and the other four cats had acceleration of VT. The average dose of Clon required to terminate the sustained VT was $62.9 \pm 5.2 \mu\text{g kg}^{-1}$ and was higher than that in Group II (62.9 ± 5.2 vs. $28.3 \pm 6.2 \mu\text{g kg}^{-1}$, $P < 0.01$).

In experimental Groups V and VI, Yoh (0.05 mg kg^{-1} i.a.) was administered at 5 min after discontinuing AS infusion and Clon was given via i.v. (Group V) or i.a. (Group VI) injection to terminate VT. Acceleration of VT with rapid degeneration into ventricular fibrillation leading to cardiac arrest within 5 min after i.a. Yoh were seen in two of ten cats (one each in group V or VI). The other eight cats had acceleration of VT after i.a. Yoh. Figure 6 shows typical tracings from a cat in Group VI. The average dose of Clon for termination of VT in Group VI was significantly lower than that in Group V (14.8 ± 3.7 vs. $88.5 \pm 16.3 \mu\text{g kg}^{-1}$, $P < 0.01$). The average dose of Clon for termination of VT in Group V was significantly higher than that in Group II ($P < 0.01$). The average Clon dose for termination of VT in Group VI was significantly higher than that in Group III ($P < 0.01$).

Effects of clonidine on blood pressure

Immediately after VT was converted by administration of Clon to sinus rhythm or junctional rhythm, the blood pressure rose slightly but then declined gradually during the observation period. In Groups II and III, Clon administration

Figure 6 Recordings show the effect of i.a. clonidine (Clon) on ventricular tachycardia (VT) induced with acetylcholinesterase inhibitor (AS) $225 \mu\text{g kg}^{-1}$, i.v. Yohimbine (Yoh 0.05 mg kg^{-1} , i.a.) administered at 5 min after discontinuation of AS in a cat from Group VI. Left upper panel recorded at slow speed. The letters a-e above the slow-speed recordings represent the times at which the corresponding fast-speed electrocardiogram and blood pressure in panels a-e were recorded. (a) VT with average tachycardia cycle length 350 ms induced with i.v. AS $225 \mu\text{g kg}^{-1}$ and i.a. Yoh 0.05 mg kg^{-1} administered at 5 min after discontinuation of AS. The first dose of i.a. Clon $1.6 \mu\text{g kg}^{-1}$ administered at arrow, did not terminate VT. (b) Average VT cycle length increased to 470 ms after Clon dose increased to $6.4 \mu\text{g kg}^{-1}$ i.a. (c) Short-run ventricular tachycardia with junctional beats seen after Clon dose increased to $8.0 \mu\text{g kg}^{-1}$ i.a. (d) Occasional ventricular premature beats with junctional beats observed after the Clon dose increased to $11.2 \mu\text{g kg}^{-1}$ i.a. (e) Recordings show sinus rhythm with secondary degree atrioventricular conduction block at 8 min after the first dose of Clon i.a.

resulted in significant decreases (50 ± 6 and 46 ± 4 mmHg, respectively) of MBP from the control values ($P < 0.01$). In Groups IV, V, and VI, although Yoh increased the antiarrhythmic dose of Clon, it did not affect blood pressure or prevent the Clon induced hypotension (MBP decrease 56 ± 10 , 52 ± 6 , and 48 ± 7 mmHg, respectively).

Discussion

Major findings

These experiments showed that Clon (i.a.) in a dose as small as one fifth to one sixth of an i.v. Clon dose could effectively terminate AS-induced VT. This antiarrhythmic effect was substantially antagonized by Yoh, an α_2 -antagonist. These findings confirm the notion of Gillis & Quest (1972), that Clon produces antiarrhythmic effects through a central action. Our results further indicate that this effect involves specifically α_2 -receptors in the central nervous system.

Electrophysiological effects of digitalis on the heart

Digitalis not only modifies the transmembrane action potential, but induces alterations in the slope of phase 4 depolarization of cells of the specialized conducting system. Digitalis intoxication causes increased intracellular sodium and calcium levels. Calcium overload mediating oscillatory release of calcium from the intracellular store is the primary event underlying the afterpotential which generates transient inward currents. Canine Purkinje fibres perfused with AS exhibited transient inward current (TI) which contributed to its arrhythmogenic activity (Kass & Lederer, 1978; Kass & Tsien, 1978).

Role of sympathetic neural activity in digitalis-induced ventricular arrhythmia

The relationship between the sympathetic nervous system and digitalis-induced ventricular arrhythmia is well established. Digitalis intoxication causes non-uniform discharges in

cardiac sympathetic nerves which might result in non-uniformity of the electrical properties of myocardial cells (Kim *et al.*, 1984). Gillis & Quest (1972) found that a toxic dose of digitalis induced an increase in the sympathetic nerve activity in the preganglionic cardiac nerve, indicating a centrally mediated effect. Exclusion of the sympathetic nervous system by cardiac denervation or spinal cord transection significantly increased the dose of digitalis needed to produce ventricular arrhythmias (Raines *et al.*, 1967). A toxic dose of deslanoside increased the concentration of a noradrenaline metabolite, and midcollicular decerebration increased the deslanoside dose required to produce ventricular arrhythmias (Helke *et al.*, 1979). Similarly, the dose of ouabain needed to produce ventricular arrhythmias in cats increased two weeks after sympathectomy (Lather *et al.*, 1978). Lechat & Schmitt (1982) reported that the dose of digitalis glycoside required to produce ventricular arrhythmias was reduced by Yoh, an α_2 -adrenoceptor antagonist. Yoh enhanced sympathetic outflow to the heart might contribute to the aggravation of digitalis-induced VT. On the other hand, inhibition of the release of neurotransmitters may be the contributory factor for the antiarrhythmic activity of Clon on AS-induced VT.

Site of effect of clonidine on digitalis-induced ventricular tachycardia

Several studies strongly indicate that the central nervous system is the primary site of antiarrhythmic action of Clon. Gillis & Quest (1972) provided several pieces of evidence to indicate that the antiarrhythmic effect of Clon was through the central adrenergic system. Firstly, Clon simultaneously converted VT and depressed sympathetic nerve discharge. A dose of Clon that did not depress nerve firing did not restore normal sinus rhythm and *vice versa*. Only when sympathetic nerve firing was depressed did Clon restore cardiac rhythm to normal. Secondly, Clon lost its antiarrhythmic effect in cats when their sympathetic nervous systems were interrupted by section of the spinal cord. If the antiarrhythmic effect of Clon was through a direct effect on myocardial cells, spinal section should not alter its antiarrhythmic effect. Lechat & Schmitt (1982) reported that α_2 -adrenoceptor stimulation with Clon reduced the arrhythmogenic effects of ouabain, whereas no protection was found with ST 91, a Clon-related compound which does not cross the blood-brain barrier. All the above findings indicate that the ventricular arrhythmias induced by digitalis and its related compounds is due in part to stimulation of the central nervous system leading to an increase in sympathetic nervous activity and that the antiarrhythmic effect of Clon might be mediated through central α_2 -adrenoceptors. These notions were confirmed in the present experiments. The dose of Clon via i.a. administration ($5.8 \pm 1.0 \mu\text{g kg}^{-1}$) which could suppress the AS-induced VT was only about one-fifth or one-sixth of the dose required by the i.v. route ($28.3 \pm 6.2 \mu\text{g kg}^{-1}$). This dose could also inhibit VT (referred to experiments in Groups II and III). As a small i.a. dose, if administered via the i.v. route, was not effective in suppressing the VT, it is suggested that Clon is not acting peripherally but rather has a primarily central action. Furthermore, following interaction with Yoh (either 0.5 mg kg^{-1} , i.v. in Group IV; or 0.05 mg kg^{-1} , i.a., in Groups V and VI), the dose of Clon required (i.v. or i.a.) to suppress VT was greatly increased. These findings indicate that the antiarrhythmic effect of Clon may specifically involve the α_2 -adrenoceptor in the central nervous system.

However, Clon is not completely lacking in direct effects on the heart. Rosen & Weiss (1984) found in an *in vitro* experiment, that Clon 1×10^{-6} and $1 \times 10^{-5} \text{ M}$ significantly reduced V_{max} and prolonged the action potential duration of driven canine Purkinje fibres. Since these actions were not blocked by Yoh or by prazosin, a direct membrane effect not involving the adrenoceptor was suggested. However, the present study not only provides no evidence to indicate the importance of direct effects on the heart but rather suggests

that such direct cardiac effects may not be essential. Thus, while a small dose of Clon administered i.v. did not suppress the VT, the same dose given i.a. converted it to sinus rhythm.

Clinical implication

Digitalis has been commonly used for many years to treat heart failure and cardiac arrhythmias, such as atrial fibrillation with rapid ventricular response and paroxysmal supraventricular tachycardia. However, ventricular arrhythmias frequently result from digitalis intoxication caused by high myocardial digitalis concentration or central digitalis effects. Current therapy for these ventricular arrhythmias consists primarily of digitalis withdrawal along with the use of conventional antiarrhythmic agents, such as lignocaine and phenytoin. The action of these drugs is thought to be a direct suppression of the enhanced myocardial automaticity. In the present study, the antiarrhythmic effect of Clon on AS-induced VT was probably mediated through central

α_2 -adrenoceptors. Our findings suggest an additional avenue for treatment of digitalis-induced VT. However, use of Clon in human subjects with cardiovascular disease has been reported to produce sinus bradycardia, sinus arrest and hypotensive events. Much attention must be given to optimizing dose schedules and minimizing potential side effects before clinical use in human subjects could be recommended. However, the most effective therapy for digitalis-induced arrhythmias is a preparation of digitalis specific antibody fragments (e.g. Digibind or Digitalis antidote BM). On the other hand, drugs possessing central α_2 -adrenoceptor antagonistic effect, such as Yoh, should be used carefully to avoid potentiating the occurrence of digitalis-induced VT.

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