Central Effects of Paraoxon on Haemodynamics in the Cat

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Summary. Application of paraoxon into the left vertebral artery (8–80 μg) or both the left and right vertebral artery (4–8 μg) of the anaesthetized cat evoked dose-dependent depressor effects, whereas heart rate was not influenced significantly. Also after systemic administration of paraoxon (150–825 μg·kg⁻¹), while peripheral muscarinic receptors were blocked, depressor effects were still observed. Dose-response curves for the depressor response to paraoxon were established. Infusion of low doses of dexetimide via the vertebral artery prevented the hypotensive action of paraoxon. The distribution of this antimuscarinic drug in the brain was investigated. The depressor effect of paraoxon can be attributed to both a decrease in peripheral resistance and cardiac output. Decerebration and midcollicular transection were carried out in order to elucidate the site and mechanism of action. The depressor effect of paraoxon seems to be mediated by a central mechanism of action located within the lower brain stem.

It is concluded that stimulation of muscarinic receptors in the pontomedullary region gives rise to the observed changes in haemodynamic parameters. Muscarinic receptors in the hypothalamus seem to be of minor importance for the hypotensive action of paraoxon.

Key words: Paraoxon — Blood pressure — Vertebral artery — Central muscarinic receptors — Cat

Introduction

Although ample evidence has been presented for the involvement of central adrenergic mechanisms in the regulation of blood pressure, less attention has been paid to a possible role of brain acetylcholine in the control of haemodynamics. A number of authors studied the effects of centrally administered muscarinic-like agents and acetylcholinesterase inhibitors on the cardiovascular system. However, variable effects have been reported.

In normotensive rats pressor responses to sarin (Dirnhuber and Cullumbine 1955), physostigmine (Varagic and Krstic 1966), oxotremorine, pilocarpine and arecoline (Dage 1979) as well as biphasic responses to carbachol, neostigmine (Brezenoff 1972) and physostigmine (Brezenoff and Rusin 1974) have been observed and attributed to a central action of the drugs.

Administration of sarin (Stewart and Anderson 1968) or soman (Preston and Heath 1972) into rabbits evoked depressor effects. In dogs sarin, tabun (Heymans et al. 1956; Brown 1960), acetylcholine and methacholine (Lang and Rush 1973) induced excitatory, whereas oxotremorine, pilocarpine and arecoline (Dage 1979) initiated inhibitory effects on haemodynamics.

Upon central application into the cat acetylcholine, carbachol, oxotremorine, pilocarpine (Tangri et al. 1977; Bhargava et al. 1978) and arecoline, muscarine and oxotremorine (Philippu and Bohuschke 1978) evoked biphasic effects on blood pressure. On the other hand it has been demonstrated that arecoline (Porsius et al. 1978), oxotremorine, pilocarpine (Dage 1979) and physostigmine (de Wildt 1980) decrease arterial pressure in the cat.

The discrepancy in results might be attributed to differences in animal species, application techniques, to different anaesthetic agents, amounts of drugs used. Moreover, differences in the kind of cholinergic drugs might contribute to the variety of effects measured.

The present study deals with the centrally induced pharmacological effects of paraoxon on haemodynamics in the cat after both intravenous administration and infusion of the drug via the vertebral artery.

Although a number of authors studied the biological effects of paraoxon already, the majority of investigations concerns toxicological studies. Small doses of paraoxon were applied in our study.

Materials and Methods

Mongrel cats (total number: 132) of either sex (weight 2–4 kg) were anaesthetized with 60 mg α-glucocloralose·kg⁻¹ i.p. The animals were subjected to artificial respiration throughout the experiment. A femoral vein was cannulated for the i.v. administration of drugs. Blood pressure was recorded continuously from a cannulated femoral artery via a pressure transducer (Statham P23), connected to a Hellige recorder. Heart rate was established from pulse waves in the femoral artery.

Administration Via the Vertebral Artery. For the administration of drugs via the left vertebral artery (v.a.) the left subclavian artery was exposed after left-sided thoracotomy and all side-branches except the left v.a. were ligated. A catheter was inserted into the distal end of the subclavian artery and pushed forward until its tip lay just distal to the ostium of the left v.a. Therefore, drugs injected through the catheter will enter the left v.a. and will be transported to the romboencephalon. A detailed description of this technique has been published previously (van Zwieten 1975).

For the infusion of drugs via both the left and right v.a. right-sided thoracotomy was carried out as well. The right subclavian artery was cannulated in a similar manner as described above. The catheters from both subclavian arteries were connected to syringes, placed in appropriate infusion pumps (Braun, Melsungen, FRG). A detailed description of this animal model has been published recently (Porsius 1980).
Use of the Electromagnetic Flowmeter. For the measurement of various haemodynamic parameters the ascending aorta was exposed after left-sided thoracotomy. A flow probe with an appropriate diameter (5–7 mm) was placed on the root of the aorta and velocity of blood was measured by means of a calibrated electromagnetic flowmeter (Transflow-601, Skalar Instruments, Delft, Holland). Various parameters were determined according to the technique described by Hughes (1970). Phasic aorta flow was recorded on a Hellige recorder. Left ventricular stroke volume was recorded by integrating the flow velocity signal. Cardiac output (less coronary flow) was calculated from stroke volume and cardiac frequency. A beat-by-beat recording of maximum acceleration of blood from the left ventricle was obtained by differentiating the velocity signal. This parameter is an index myocardial contractile force (Noble et al. 1966). Total peripheral resistance was calculated from mean arterial pressure (MAP) and cardiac output. The validity of the method has been summarized by Hamilton et al. (1966).

Decerebrated Animals. In a number of experiments paraoxon was tested in pithed cats. A hole was drilled 1–2 cm rostral to the orbita and a pithing rod was pushed forward through the vertebral canal. Vagal outflow was prevented by bilateral cervical vagotomy. When necessary blood pressure of these animals was increased to normal levels by means of a noradrenaline infusion (1.7 µg·kg⁻¹·min⁻¹). In separate experiments midcollicular transection was carried out according to a method described by Koller and Jenny (1969).

Drug Distribution in CNS. For the determination of 3H-dextemizide in brain tissue the animals were killed by occlusion of the ascending aorta 2 min after the simultaneous administration of the drug via the left and right v.a. Various brain regions were isolated and weighed. To each 100 mg of brain tissue 1 ml of methanol was added. After homogenization and centrifugation 10 ml Instagel (Packard Instrument Company, Caversham, England) were added to an aliquot of the supernatant. Total radioactivity was measured by means of a liquid scintillation counter (Isocap 300). A correction was made for quenching by using an external standard. Blood pressure was calculated as mean arterial pressure (MAP). Statistical analysis was carried out by means of Student’s t-test; P < 0.05 was considered to be significant. For the calculation of the amount of drug for i.v. administration body-weights were taken into account. However, when drugs were given via the v.a. the infused dose was independent on body weight (absolute amount). Mean body weight amounted to 2.8 ± 0.1 kg (n = 50).

Drugs Used. α-Glucochloralose (E. Merck, Darmstadt, FRG), paraoxon (Sigma Chemical Company, St. Louis, MO, USA), N-methylatropinium nitrate (E. Merck, Darmstadt, FRG), galamine triethiodide (Sigma Chemical Company, St. Louis, MO, USA), piperoxane HCl (Janssen Pharmaceutical, Beerse, Belgium), metoprolol HCl (Hässle AB, Mölndal, Sweden), mecamylamine HCl (Sigma Chemical Company, St. Louis, MO, USA), dextemizide HCl (= d-benzethimide HCl) (Janssen Pharmaceutical, Beerse, Belgium), 3H-dextemizide (ibid.; 3H label in ortho-position of the benzyl group; specific activity: 15.2 Ci per mmol), arecoline HBr (E. Merck, Darmstadt, FRG), clonidine HCl (Boehringer, Ingelheim, FRG).

Paraoxon was dissolved in dimethylformamide (DMF). Before administration the solution was diluted with saline in such a manner that the final injection fluid contained not more than 3% DMF. All other drugs were dissolved in saline. In control experiments it was established that neither saline, nor DMF (3% in saline) influenced haemodynamics upon i.v. or “central” infusion. In all experiments total volume of the administered drug solutions amounted to 140 µl which were always infused during 1 min (infusion pump Braun, Melsungen, FRG).

Results

Intact, Anaesthetized Cats

MAP and heart rate of the anaesthetized cats amounted to 124 ± 3 mm Hg and 165 ± 4 beats per min respectively (n = 50). In order to prevent the peripherally induced phar-