Reversal of experimental hemorrhagic shock by dimethylphenylpiperazinium (DMPP)

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Abstract. In a rat model of hemorrhagic shock which caused the death of all control rats within 30 min, i.v. injection of the ganglion-stimulating drug dimethylphenylpiperazinium (DMPP) caused a dose-dependent reversal of the shock condition – without the need for reinfusion of the shed blood – starting from the dose of 4 ng/kg i.v. Shock reversal was associated with the mobilization of residual blood and improvement in blood flow, particularly at the carotid level. These results could influence our thinking on pathophysiology and first-aid management of shock.
Key words. Hypovolemic shock; hemorrhage; dimethylphenylpiperazinium; resuscitation.

Rapid exsanguination or hemorrhagic shock is the principal cause of death outside the hospital in victims of civilian [1] or military [2, 3] trauma. The depth and duration of trauma-induced hemorrhagic shock is a major factor in subsequent in-hospital mortality rates. Measures taken in the field to prevent profound and prolonged hypotension before fluid resuscitation with i.v. blood or plasma substitutes becomes available are therefore of key importance in increasing survival [4].

Previous studies have shown that in experimental and clinical hemorrhage-induced hypovolemic shock, the timely i.v. injection of melanocortin (ACTH-MSH) peptides in pharmacological doses (40–160 μg/kg) induces a prompt and sustained restoration of blood pressure and pulse amplitude [5–10], greatly prolongs survival, and extends the time-limit for effective blood reinfusion [11]. Available data indicate that the melanocortin-induced shock reversal occurs through the activation of a polysynaptic vasomotor reflex, eventually causing the mobilization of the peripherally-pooled residual blood, with restoration of the tissue blood flow and normalization of venous pO_2 [12–15]. Indeed, shock reversal is largely prevented by a) bilateral vagotomy at the cervical level [16], b) the blockade of brain muscarinic receptors with 4-diphenylacetoxy-N-methylpiperidine methobromide (but not with AF-DX 116 or pirenzepine, which suggests the involvement of the M_3 subtype receptors) [17, 18], c) the intracerebroventricular injection of hemicholinium-3 [19] (which produces a functional blockade of cholinergic neurons), d) ganglion-blocking drugs (unpublished data), e) reserpine and guanethidine [20] (which produce a functional blockade of adrenergic neurons), and f) the blockade of peripheral α_1 and α_2 adrenoceptors [20]. Moreover, the anti-shock effect of melanocortins is greatly impaired in splenectomized animals and in animals subjected to ligature of the suprahepatic veins [12, 13] (that is, when major blood reservoirs are excluded).

Since the final step of the complex vasomotor reflex triggered by melanocortins in conditions of shock is the activation of postganglionic sympathetic neurons [20], we have investigated the effect of a typical ganglion-stimulating drug – dimethylphenylpiperazinium, DMPP – in an experimental model of hemorrhage-induced hypovolemic shock.

Materials and methods

Adult Wistar rats of either sex (230–280 g) were used. Under anesthesia with ethylurethane (1.25 g/kg i.p.) and after heparinization (heparin sodium 600 IU/kg i.v.), indwelling catheters were implanted in a common carotid artery and in an iliac vein. Systemic blood pressure and pulse pressure (PP) were recorded by means of a pressure transducer (Statham P23 Db) connected to a polygraph (Battaglia–Rangoni, Bologna, Italy). Heart rate (HR) was recorded and calculated by the same polygraph. Respiratory rate (RR) was recorded by means of three electrodes subcutaneously implanted on the chest and connected to the polygraph through an ARI A380 preamplifier. MAP (diastolic pressure plus one third of PP) was automatically calculated and continuously digitally displayed by the polygraph. Volume-controlled hemorrhagic shock was induced by stepwise bleeding until MAP stabilized around 20–24 mm Hg (basal, prebleeding value: 71–102 mm Hg). A total volume of 2.23 ± 0.15 (mean ± SEM) ml of blood per 100 g b.wt was withdrawn over a period of 25–30 min. After 5 min of stabilization, rats received an i.v. bolus injection either of DMPP (4, 20, 100 or 500 ng/kg) or of 0.9% NaCl, in a volume of 1 ml/kg. MAP, PP, HR and RR were recorded for 2 h after treatment, or until prior death.

At the end of the 2-h observation period, animals treated with the highest dose of DMPP (500 ng/kg i.v.) had their surgical wounds sutured, were allowed to recover from anesthesia, and were then maintained under standard conditions, one per cage, in the colony rooms where they were observed with no other treatment until death, or for a maximum of 15 days, to determine total survival time.

The effect of DMPP was also studied in conscious rats. Two to three days before the start of experiment, heparinized catheters were implanted, under ethyl-ether anesthesia, in a common carotid artery for recording arterial blood pressure and in an iliac vein for bleeding and i.v. injections. The catheters were guided s.c. to the neck where they were exteriorized, filled with 0.9% NaCl and closed with metal plugs. At the time of the experi-

ment, the rat was placed in a small plastic cage (20 × 10 × 10 cm) with a grid lid, and the arterial catheter was connected to the pressure transducer. Stepwise bleeding was performed as previously described through the venous catheter, and when MAP fell to, and stabilized at, 20–24 mm Hg, the rats where randomly given i.v. either 500 ng/ml/kg DMPP (n = 6) followed by 0.5 ml of washing saline, or an equal volume of saline (n = 6). The MAP was recorded for 1 h, or until prior death. Thereafter, the catheters were permanently closed and sutured under the skin, and the animals were placed in single cages with food and water freely available, without any other treatment, and kept under observation for survival time for a maximum of 15 days.

In one set of experiments (n = 6), complete bilateral vagotomy was performed at the cervical level by tying two silk sutures around each vagal trunk, one above the other, and transecting each trunk between the sutures; the sutures served to ensure complete transection and to facilitate postmortem verification of disconnection. In some rats (n = 10), the carotid body area was surgically exposed, and the region of the bifurcation was infiltrated with a solution of 1% lidocaine HCl, 10–15 min before treatment.

In order to define the possible role of the adrenal glands, a group of animals (n = 10) was bilaterally adrenalectomized, under ethyl-ether anesthesia, by the abdominal route 1 week before the experiment. Thereafter, these rats were given saline instead of tap water to compensate for the absence of mineralocorticoid regulation of sodium balance.

The volume of residual circulating blood was measured using the dilution principle according to Wang[21]: 0.1 ml of a 0.451% solution of Evans blue was injected into the rat 2–3 min after treatment and blood sampling was carried out 5 min thereafter.

Blood flow was measured at the level of a common carotid artery, of the portal vein and of the abdominal cava, with a miniaturized 20-MHz pulsed Doppler probe consisting of a piezoelectric crystal housed in a soft silastic suction cup, placed around the vessel (0.75, 1.5 and 1.5 mm i.d. for carotid, portal vein and abdominal cava respectively). The flow probes were connected to a flowmeter (Crystal Biotech, Holliston, MA, USA). Pulsatile and mean Doppler shifts (kHz) were recorded simultaneously on the Battaglia–Rangoni polygraph. Velocities were calculated from the measured Doppler shifts using the Doppler equation in the conventional manner[22], and estimates of volume flow were obtained by multiplying the mean velocity by the estimated internal cross-sectional area.

The following drugs were used: dimethylphenylpiperazinium iodide, hexamethonium chloride, atropine methylbromide (Sigma Chemicals Co., St. Louis, USA); guanethidine sulphate (Ciba-Geigy, Basel, Switzerland); dibenamine HCl (ICN Pharmaceuticals, New York, USA); atenolol (Imperial Chemical Industries, Milan, Italy).

Calculations and statistics

All data are given as mean ± SEM. MAP and PP of all groups were first compared with each other by means of an analysis of variance (ANOVA), separate comparisons being made for data obtained before bleeding, after bleeding, 15–20 min and 120 min after treatment. In the case of after-treatment data, ANOVA was followed by Dunnett's test for multiple comparisons with a control. Blood flow, volume of residual circulating blood, total survival times, HR and RR were analyzed by Student's t-test, and survival rates by Fisher's exact probability test.

Results and discussion

This model of volume-controlled hemorrhagic shock was used instead of the more widely-used pressure-controlled one[23–26] because the former is closer to the clinical condition, whereas the latter – which includes late partial reuptake of blood, thereby eliminating the animal's natural response – is unphysiologic and not clinically relevant[27,28]. Bleeding to a MAP of about 20–24 mm Hg also changed PP, RR and HR. PP, which was 40–50 mm Hg before bleeding, stabilized around 10 mm Hg during shock; RR, which was 90–110 breaths/min before bleeding, fell to 40–45 breaths/min; HR slowed from 300–360 beats/min before bleeding to 220–280 beats/min. All rats treated with saline died within 30 min, while rats treated with DMPP showed a prompt, dose-dependent improvement in cardiovascular and respiratory functions. The dose of 500 ng/kg practically restored these functions (RR: 70 ± 4 breaths/min; HR: 308 ± 10 beats/min; in both cases: n = 10, $p < 0.001$ versus the corresponding value of saline-treated rats, Student's t-test), and those treated with 20 ng/kg or more were all still alive 2 h after treatment (table 1).

In normovolemic, non-bled rats, the minimum i.v. dose of DMPP causing a significant increase in arterial pressure was 200 µg/kg, that is 10,000 times higher than the dose causing 100% survival in hemorrhage-shocked animals (data not shown).

The mean survival time was 225 ± 60 h in rats treated with 500 ng/kg of DMPP (n = 10; 6 rats survived at least 15 days; $p < 0.001$, Student's t-test), compared to 24 ± 4 min in saline-treated rats (n = 10). An even more impressive result was obtained in conscious rats, likewise bled to hypovolemic shock: while all control (saline-treated) rats died within 40 ± 6 min after treatment, all rats treated with 500 ng/kg of DMPP were still alive 15 days after the experiment ($p < 0.001$, Student's t-test).

DMPP-induced shock reversal was associated with a massive increase in the volume of residual circulating blood (1.31 ± 0.20 and 2.64 ± 0.14 ml/100 g b.wt in saline-treated rats and in rats treated with 500 ng/kg

Table 1. Effect of the ganglion-stimulating agent dimethylphenylpiperazinium iodide (DMPP) in bleeding-induced hypovolemic shock, in rats. MAP = mean arterial pressure. PP = pulse pressure. The after-treatment values are the means ± SEM for survived rats only. ANOVA of MAP and PP values of all groups before treatment (= before and after bleeding) gave p values > 0.05; after treatment gave p values < 0.001.

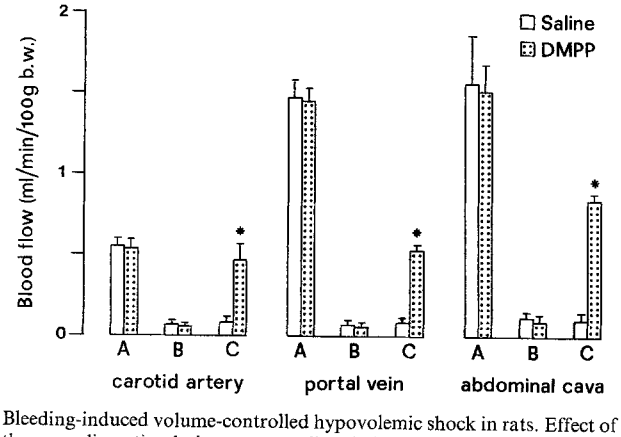
Treatment (μg/kg i.v.)	MAP / PP (mm Hg; mean ± SEM)				No. of rats still surviving 120 min after treatment/ No. of treated rats
	Before bleeding	After bleeding	15-20 min after treatment	120 min after treatment	
Saline	90 ± 5 / 45 ± 4	22 ± 1 / 10 ± 1	24 ± 3 / 10 ± 3	0 / 0	0/10
DMPP, 0.004	79 ± 9 / 39 ± 3	21 ± 1 / 9 ± 1	32 ± 5 / 19 ± 6	35 ± 4* / 26 ± 3*	4/8**
DMPP, 0.020	89 ± 4 / 40 ± 2	22 ± 1 / 11 ± 1	51 ± 4* / 33 ± 4*	40 ± 6* / 28 ± 3*	8/8***
DMPP, 0.100	91 ± 6 / 36 ± 4	23 ± 1 / 10 ± 2	59 ± 8* / 37 ± 6*	55 ± 5* / 33 ± 4*	8/8***
DMPP, 0.500	82 ± 5 / 45 ± 4	22 ± 1 / 12 ± 2	78 ± 4* / 45 ± 5*	80 ± 6* / 45 ± 5*	10/10***
DMPP, 2.5	82 ± 6 / 45 ± 2	22 ± 1 / 9 ± 1	64 ± 1* / 39 ± 3*	60 ± 3* / 40 ± 4*	8/8***

* $p < 0.001$ versus the corresponding value of saline-treated rats (Dunnett's test) ** $p < 0.025$ and *** $p < 0.005$ versus the corresponding value of saline-treated rats (Fisher's test).

DMPP, respectively; n = 7 in both cases; $p < 0.001$, Student's t-test).

Capillary pooling and trapping of blood, and prolonged transit time – with consequent decreased tissue perfusion and venous return – characterize the terminal phase of shock. The increase in circulating blood volume induced by DMPP in shocked rats seems to be the consequence of a mobilization of the peripherally-pooled residual blood, with consequent improvement of tissue perfusion. Indeed, DMPP caused a significant increase in blood flow in different vascular beds, particularly at the carotid level (fig.).

None of the pharmacological pretreatments (table 2) or the sham experimental conditions (data not shown) significantly modified the outcome of the shock in saline-treated animals. Moreover, no sham experimental condition had any significant influence on the effect of DMPP (data not shown).



Bleeding-induced volume-controlled hypovolemic shock in rats. Effect of the ganglion-stimulating agent dimethylphenylpiperazinium iodide (DMPP, 500 ng/kg i.v.) on the mean blood flow at the level of a common carotid artery, the portal vein and the abdominal cava. Means ± SEM from 10 rats per group. A: before bleeding (basal condition); B: after bleeding (shock); C: 15–20 min after treatment. * $p < 0.001$ versus the corresponding value of saline-treated rats (Student's t-test).

DMPP-induced shock reversal was almost completely antagonized by the ganglion-blocking drug hexamethonium (table 2), while atropine methylbromide merely prevented complete restoration of the arterial pressure, without affecting the effect of DMPP on PP and on survival rate. However the main site of action of DMPP seems to be at the carotid body chemoreceptors, for the bilateral anesthetization of this area completely prevented its anti-shock effect (table 2). It would therefore appear that, like nicotine and protoveratrines[29,30], DMPP reverses hemorrhagic shock through the activation of a polysynaptic reflex starting from arterial chemoreceptors. The final steps obviously involve post-ganglionic sympathetic neurons: the anti-shock effect of DMPP was indeed antagonized by the functional blockade of these neurons with guanethidine. The main target organ seems to be the heart, because the action of DMPP was more effectively antagonized by β_1- (atenolol) than by α_1 (dibenamine) adrenoceptor blockade (table 2).

An essential role in the anti-shock effect of DMPP is played by the adrenal glands: indeed, adrenalectomy completely abolished the anti-shock effect of DMPP 500 ng/kg i.v. (table 2). Since DMPP is a ganglion-stimulating drug, it is most likely that the lack of effect of DMPP in adrenalectomized rats is because these animals can no longer release adrenaline and not because of the absence of gluco- and mineralocorticoids. Thus, in the mechanism of action of DMPP-induced shock reversal, adrenaline apparently plays a role as important as that of noradrenaline. The function of postganglionic sympathetic nerves is essential as well, since guanethidine – which has no effect on adrenal glands at doses that cause

Table 2. Influence of various pretreatments or different experimental conditions on the anti-shock effect of DMPP, in rats. MAP = mean arterial pressure. PP = pulse pressure. Bilateral vagotomy at the cervical level was performed 2 min before starting bleeding. Carotid body anesthetization was performed 10–15 min before treatment. Bilateral adrenalectomy was performed 7 days before the experiment. Atropine methylbromide, guanethidine, dibenamine and atenolol were administered 2, 2, 60 and 2 min before bleeding, respectively; hexamethonium was administered 10–15 min before treatment. All injections were in a volume of 1 ml/kg b.wt. The after-treatment values are the means ± SEM for survived rats only. ANOVA of MAP and PP values of all groups before treatment (= before and after bleeding) gave p values > 0.05; after treatment gave p values < 0.001.

Pretreatment (mg/kg) or experimental condition	Treatment (µg/kg i.v.)	MAP / PP (mm Hg; mean ± SEM)				No. of rats still surviving 120 min after treatment/ No. of treated rats
		Before bleeding	After bleeding	15–20 min after treatment	120 min after treatment	
Saline	Saline	88 ± 6 / 43 ± 2	22 ± 1 / 10 ± 1	25 ± 2* / 12 ± 2*	0* / 0*	0/10***
Saline	DMPP, 0.5	86 ± 6 / 46 ± 2	21 ± 1 / 10 ± 1	84 ± 3 / 44 ± 3	80 ± 3 / 46 ± 4	10/10
Bilateral vagotomy	Saline	90 ± 5 / 40 ± 3	24 ± 2 / 11 ± 1	25 ± 2* / 12 ± 2*	0* / 0*	0/8***
Bilateral vagotomy	DMPP, 0.5	93 ± 7 / 60 ± 5	22 ± 1 / 13 ± 1	63 ± 5* / 57 ± 4	60 ± 6* / 55 ± 5	6/6
Carotid bodies anesthetization	Saline	87 ± 4 / 43 ± 3	20 ± 2 / 9 ± 1	22 ± 2* / 11 ± 2*	0* / 0*	0/6***
Carotid bodies anesthetization	DMPP, 0.5	102 ± 8 / 45 ± 5	22 ± 1 / 11 ± 1	23 ± 1* / 12 ± 2*	0* / 0*	0/10***
Atropine methylbromide,2 i.p.	Saline	95 ± 6 / 47 ± 4	23 ± 2 / 12 ± 2	25 ± 3* / 14 ± 3*	0* / 0*	0/6***
Atropine methylbromide,2 i.p.	DMPP, 0.5	96 ± 8 / 41 ± 3	23 ± 1 / 14 ± 2	48 ± 8* / 37 ± 5	45 ± 6* / 38 ± 5	8/8
Hexamethonium,2 i.p.	Saline	85 ± 4 / 45 ± 2	22 ± 1 / 13 ± 2	24 ± 2* / 15 ± 3*	0* / 0*	0/6***
Hexamethonium,2 i.p.	DMPP, 0.5	81 ± 5 / 47 ± 2	24 ± 1 / 14 ± 1	31 ± 2* / 20 ± 3*	15/27 / 10/18	2/6**
Guanethidine,10 i.p.	Saline	92 ± 4 / 43 ± 3	21 ± 2 / 10 ± 2	24 ± 3* / 12 ± 3*	0* / 0*	0/6***
Guanethidine,10 i.p.	DMPP, 0.5	96 ± 5 / 45 ± 3	20 ± 2 / 9 ± 1	23 ± 2* / 14 ± 3*	0* / 0*	0/10***
Bilateral adrenalectomy	Saline	92 ± 7 / 47 ± 5	23 ± 2 / 10 ± 1	25 ± 3* / 12 ± 2*	0* / 0*	0/6***
Bilateral adrenalectomy	DMPP, 0.5	96 ± 9 / 51 ± 3	24 ± 1 / 10 ± 1	27 ± 3* / 13 ± 3*	0* / 0*	0/10***
Dibenamine,15 i.v.	Saline	78 ± 4 / 44 ± 4	22 ± 1 / 12 ± 2	24 ± 2* / 14 ± 3*	0* / 0*	0/6***
Dibenamine,15 i.v.	DMPP, 0.5	71 ± 5 / 42 ± 5	21 ± 1 / 13 ± 2	33 ± 3* / 25 ± 7*	30 ± 5* / 22 ± 5*	8/8
Atenolol,2 i.v.	Saline	80 ± 7 / 43 ± 5	20 ± 2 / 10 ± 2	23 ± 3* / 12 ± 3*	0* / 0*	0/5***
Atenolol,2 i.v.	DMPP, 0.5	86 ± 9 / 41 ± 6	20 ± 1 / 11 ± 2	34 ± 6* / 21 ± 4*	18/29 / 12/20	2/6**
Dibenamine,15 i.v. plus atenolol,2 i.v.	Saline	78 ± 5 / 40 ± 5	22 ± 2 / 11 ± 2	25 ± 3* / 12 ± 3*	0* / 0*	0/5***
Dibenamine,15 i.v. plus atenolol, 2 i.v.	DMPP, 0.5	76 ± 4 / 41 ± 3	21 ± 1 / 13 ± 1	32 ± 3* / 23 ± 2*	28 ± 6* / 20 ± 5*	6/8

* $p < 0.01$, at least, versus the corresponding value of saline-pretreated and DMPP-treated rats (Dunnett's test). ** $p < 0.025$ and *** $p < 0.005$ versus the corresponding value of saline-pretreated and DMPP-treated rats (Fisher's test).

a functional blockade of sympathetic neurons – completely prevented the anti-shock effect of DMPP in non-adrenalectomized rats.

Both speculative and practical conclusions can be drawn from these results. The availability of drugs which, at extremely low, nearly atoxic doses, are able to restore for hours the cardiovascular and respiratory functions and the perfusion of vital organs, is clearly of practical importance in the first-aid treatment of hemorrhagic shock. From a speculative point of view, these results suggest that in life-threatening conditions of extreme hypotension, such different drugs as melanocortin peptides and

DMPP may be able to trigger, through different mechanisms, a poorly-characterized reflex starting from vascular chemo- and/or pressoreceptors which eventually restores tissue perfusion to a point compatible with survival. Such receptors are apparently greatly sensitized in conditions of hypovolemic shock, since they can be activated by the above drugs at doses that are almost ineffective under normal conditions.

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Catecholamine metabolism in the vas deferens and the adrenal gland with special reference to the central catecholamine-depleted state

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Abstract. Experiments were carried out to elucidate the role of central catecholamines in regulating catecholamine metabolism in the vas deferens and adrenal gland of the rat. Rats were injected intracerebroventricularly (i.c.v.) with either vehicle or 6-hydroxydopamine (6-OHDA). Groups of animals pretreated with vehicle or 6-OHDA (i.c.v.) were injected intraperitoneally (i.p.) with alpha-methyl-para-tyrosine (AMT), a tyrosine hydroxylase inhibitor. Catecholamine turnover rates were estimated by determining norepinephrine or epinephrine content after administrating AMT.

Central norepinephrine and dopamine contents decreased significantly ($p < 0.05$) after treatment with 6-OHDA and AMT. The norepinephrine content of the vas deferens of rats pretreated with 6-OHDA was markedly reduced ($p < 0.001$) after administration of AMT, whereas that of the vehicle-treated rats remained unchanged. Administration of 6-OHDA had no effect on the norepinephrine or epinephrine content of the adrenal gland.

The present results indicate that central monoaminergic neurons have an inhibitory effect on the adrenergic neurons of the vas deferens. In contrast, this inhibitory regulation does not appear to be exerted on the adrenal glands.
Key words. Catecholamine; vas deferens; adrenal gland; 6-hydroxydopamine; alpha-methyl-para-tyrosine.