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# Nimodipine Affects the Microcirculation and Modulates the Vascular Effects of Acetylcholinesterase Inhibition

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## ABSTRACT

The present investigation was undertaken in order to study whether microvascular effects of the calcium antagonist nimodipine induces changes that can explain an increased detoxification of the highly toxic cholinesterase inhibitor soman. Anaesthetised, tracheotomised and artificially ventilated rats were treated intra-peritoneally (ip) with nimodipine, 10 mg $kg^{-1}$ or vehicle followed one hour later by the exposure to 45 µg $kg^{-1}$ soman (iv). Nimodipine per se induced a vasodilation in the intestine, myocardium and other muscles. In the abdominal skin soman elicited a significant vasoconstriction that was turned into an increased blood flow after nimodipine pre-treatment. A slight vasoconstriction in diaphragm of soman intoxicated rats was turned into a significant vasodilation by nimodipine pre-treatment. In the intestinal parts no effect of soman was detected. However, in nimodipine pre-treated animals soman induced a significant vasoconstriction. The capacity of soman detoxifying processes, i.e. enzymatic hydrolysis and covalent binding to different esterases, is unequally distributed throughout the body.

Together with the knowledge of the detoxifying processes of cholinesterase inhibition the results support our theory, that nimodipine alters the peripheral blood flow in a beneficial way resulting in improved detoxification ability.

## INTRODUCTION

Soman (*O*-1,2,2-trimethylpropyl methylphosphonofluoridate), a highly toxic organophosphate, exerts its toxicity by irreversible inhibition of acetylcholinesterase (AChE). The accumulation of acetylcholine elicits effects on the circulatory system with changes in blood pressure and heart rate (HR) (1). Although the cholinergic part of the nervous system is the main target for soman poisoning, other neuro-transmitter systems are also affected (2, 3). Soman intoxication induces

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deleterious reactions in the central nervous system (CNS) which include the activation of glutamatergic receptors (4, 5).

Soman may be denoted by C(±)P(±)-soman to indicate two possible configurations, (+) and (–) around the asymmetric C and P atoms in the molecule. The highly toxic C(±)P(–)-isomers are much more persistent than the relatively non-toxic C(±)P(+)-isomers (6, 7). Soman is primarily removed from the blood by enzymatic hydrolysis and covalent binding to different esterases in the blood. Accordingly, there is a rapid metabolism and binding of soman, which regulates its detoxification. Although the soman concentration in the blood rapidly decreases (8) the effects are longlasting.

Pre-treatment with the $Ca^{2+}$ antagonist nimodipine significantly decreased the soman concentration in the blood during the first minute after exposure (9). The time until signs of intoxication and death occur is increased in nimodipine pre-treated mice as compared to control animals (10). Nimodipine has effects on both cerebral and peripheral vessels (11, 12) and seems to favour the capillary (nutrient) blood flow at the expense of the non-nutrient blood flow, especially in the skeletal muscles (13, 14). Nimodipine is also reported to attenuate brain damage from ischemia (15), intracranially administered NMDA (16) and high doses of pilocarpine, a cholinergic agonist (17). Nimodipine is clinically used to prevent and treat cerebrovasospasm in subarachnoid haemorrhage.

Observing increased detoxification of soman by nimodipine pre-treatment (9), the question arose whether blood flow, altered by nimodipine, was the cause of the increased rate of detoxification. This hypothesis was examined by studying the effects of nimodipine on the regional blood flow in soman intoxicated rats.

## METHODS

### *General*

Male Sprague-Dawley rats, weighing 370–430 g, were purchased from M&B A/S, Ry, Denmark. The animals were acclimatized for at least 1 week, and received food and water *ad libitum* until the day of experiment. The experiments were approved by the Regional Research Ethical Committee in accordance with national laws (SFS 1988:539, LSFS 1989:41).

The animals were anaesthetised by ip administration of 120 mg $kg^{-1}$ thiobutabarbital (Inactin®, RBI, Natick, MA, USA), tracheotomised and artificially ventilated by a rodent ventilator (Harvard Apparatus, USA). The femoral arteries were catheterised for blood sampling and continuous mean arterial blood pressure (MAP) measurements using a Gould P2310 transducer (Gould Inc., Cal., USA) and an ABB SE 120 recorder (ABB Goerz AG, Vienna, Austria). One femoral vein was catheterised for the administration of soman and infusion of Ringer solution at 1.5 ml $h^{-1}$. Arterial $pO_2$, $pCO_2$ and pH were determined at intervals with an ABL 520 acid-base analyzer (Radiometer, Copenhagen, Denmark). Body temperature was recorded by a rectal thermistor and maintained at approximately 38°C using a heat-

ing pad. Heparin (Løvens kemiske Fabrik, Ballerup, Denmark) was given (500 I.U. $kg^{-1}$ iv) as an anticoagulant and pancuronium bromide (Pavulon®, Organon, Teknika, Boxtel, Holland) was administered iv (0.05–0.2 mg $kg^{-1}$) in order to induce skeletal muscle relaxation.

*Blood-flow measurement*

The microsphere method was employed to measure regional blood flow (18). A catheter was introduced into the left heart ventricle via the right carotid artery and used for administration of microspheres. The spheres were 15 µm in diameter (Du Pont®, NEN Products, Boston, MA, USA) and labelled with $^{141}Ce$, $^{113}Sn$ or $^{103}Ru$. The vascular resistance (R) is expressed as vascular resistance units (VRU) and calculated as $R = MAP\ Q_t^{-1}$, where MAP (kPa) was measured during the microsphere injection and $Q_t$ = tissue blood flow (g $min^{-1}$ per g tissue). In order to evaluate whether the changes in blood flow represent vasodilation or vasoconstriction the relative change in vascular resistance as the ratio between the changes in tissue vascular resistance at 0 and 5 minutes after soman intoxication was calculated.

*Experimental procedure*

Nimodipine, 10 mg $kg^{-1}$, (Batch No. 257496S, Bayer AG, Wuppertal, Germany), dissolved in DMSO (Fluka AB, p.a.) was given ip one hour prior to measuring the control blood flow (n=8). This dose of nimodipine has been shown to have biological effect in rats (17). Control animals (n=6) received only the vehicle, DMSO, 1 ml $kg^{-1}$. Soman was prepared at our establishment according to standard procedures and given iv (45 µg $kg^{-1}$) immediately after the control blood flow measurement. This dose corresponds to about $0.8 \times LD_{50}$ (19). The second and third blood flow measurements were conducted 5 and 15 minutes after the soman injection. After the third blood flow measurement the animals were sacrificed with a sodium pentobarbital injection (60 mg iv). Various tissues were autopsied and the radioactivity determined by gamma spectrometry. Blood flows were calculated as previously described (18).

*Statistical evaluation*

The unpaired two-tailed Student's t-test was used to compare the control group with the nimodipine group. When comparing the effects of soman 5 minutes after administration, the animal served as its own control and two-tailed paired Student's t-test was used. A difference was considered statistically significant if $p \leq 0.05$. Results are presented as means±sem.

## RESULTS

*Blood pressure, heart rate and blood gases*

MAP, heart rate (HR), arterial blood gases and acid-base status of the animals are shown in Table 1. MAP was significantly reduced ($p<0.01$) by nimodipine pre-treat-

Table 1. Cardiovascular parameters and blood gas values

| | Control (n=6) | | | Nimodipine (n=8) | | |
|---|---|---|---|---|---|---|
| | 0 min | 5 min | 15 min | 0 min | 5 min | 15 min |
| MAP (kPa) | 16.9 ±0.9 | 21.8 ±0.4 | 20.6 ±1.1 | 10.0** ±0.3 | 15.1** ±0.7 | 11.8** ±1.1 |
| HR (beart $min^{-1}$) | 391 ±18 | 431 ±16 | 436 ±18 | 386 ±10 | 418 ±10 | 407 ±12 |
| Hb ($g\ l^{-1}$) | 157.8 ±1.9 | 156.5 ±2.0 | 157.0 ±2.9 | 154.4 ±1.8 | 161.8 ±2.2 | 154.4 ±3.6 |
| Hct (%) | 48.3 ±0.6 | 47.9 ±0.6 | 48.1 ±0.9 | 47.3 ±0.5 | 49.6 ±0.7 | 47.3 ±1.1 |
| $pCO_2$ (kPa) | 4.65 ±0.10 | 4.69 ±0.06 | 4.76 ±0.06 | 4.72 ±0.08 | 4.69 ±0.09 | 4.71 ±0.05 |
| $pO_2$ (kPa) | 13.09 ±0.25 | 11.54 ±0.33 | 11.89 ±0.44 | 11.06** ±0.35 | 11.67 ±0.38 | 10.90 ±0.46 |
| pH | 7.51 ±0.01 | 7.50 ±0.01 | 7.47 ±0.01 | 7.42** ±0.01 | 7.39** ±0.01 | 7.32** ±0.02 |

Physiological parameters in control and nimodipine pre-treated animals before and 5 and 15 minutes after soman administration (45 µg $kg^{-1}$ iv). **p<0.01 control vs. nimodipine group, unpaired Student's t-test.

ment compared to control rats. Soman induced an increase in MAP in both groups. Five minutes after soman exposure, the blood pressure in control animals was elevated by 31 ± 8% (p<0.05) and in nimodipine pre-treated animals by 52 ± 9% (p<0.001). In the nimodipine pre-treated animals, the blood pressure decreased between 5 and 15 minutes after soman intoxication to 15 ± 8% above the control value, while the blood pressure was still increased in the control group by 25 ± 14%. Heart rate, $pCO_2$, Hb and hematocrit (Hct) were not affected by nimodipine pre-treatment. Soman caused a significant decrease in pH (p<0.01) of animals pre-treated with nimodipine. In the nimodipine pre-treated animals the $pO_2$ was somewhat reduced. In control rats the soman intoxication reduced the $pO_2$ to the same level as in nimodipine pre-treated rats. However, these minor changes in pH and $pO_2$ are within the normal range.

*Blood-flow measurements*

Depending on the organ, nimodipine pre-treatment induced either an increase or decrease in blood flow (Table 2). As compared to control animals, nimodipine pre-treatment elicited a statistically significant increase in blood flow (p<0.01) in the myocardium, duodenum, diaphragm, masseter and biceps muscle due to vasodilation. A vasodilation after nimodipine pre-treatment was detected in the ileum, jejunum, parotid gland, submandibular gland and tongue, where the vascular resistance significantly decreased (p<0.001–0.05) keeping the blood flow unchanged. In the abdominal skin, (p<0.001), spleen (p<0.01) and gastric muscle (p<0.05) a statis-

Table 2. Blood flow and vascular resistance in different organs

| Organ | Control (n=6) Blood-flow | Resistance | Nimodipine (n=8) Blood-flow | Resistance |
|---|---|---|---|---|
| Adrenal gland | 3.67 ± 0.33 | 4.80 ± 0.51 | 4.58 ± 0.72 | 2.49 ± 0.30 |
| Myocardium | 2.74 ± 0.58 | 7.91 ± 1.76 | 7.05*** ±1.10 | 1.60*** ± 0,17 |
| Duodenum | 2.58 ± 0.23 | 6.73 ± 0.50 | 5.14*** ± 0.71 | 2.20*** ± 0.28 |
| Jejunum | 1.98 ± 0.24 | 9.13 ± 1.08 | 2.19 ±0.24 | 5.04** ± 0.66 |
| Ileum | 0.94 ± 0.09 | 18.41 ± 1.09 | 1.19 ± 0.16 | 9.56*** ± 1.24 |
| Submandibular gl. | 0.49 ± 0.08 | 41.16 ± 8.37 | 0.64 ± 0.11 | 19.40* ± 3.70 |
| Parotid gl. | 0.20 ± 0.02 | 91.81 ± 10.34 | 0.42 ± 0.11 | 34.60*** ± 6.66 |
| Diaphragm | 0.16 ± 0.04 | 132.82 ± 26.26 | 0.58** ± 0.08 | 19.68*** ± 2.97 |
| Tongue | 0.15 ± 0.06 | 249.19 ± 100.27 | 0.36 ± 0.09 | 39.86* ± 7.12 |
| Masseter | 0.07 ± 0.01 | 248.26 ± 32.19 | 1.36** ± 0.32 | 9.40*** ± 1.38 |
| Biceps | 0.06 ± 0.02 | 597.81 ± 217.67 | 0.56** ± 0.14 | 35.15** ± 12.58 |
| Kidney ctx | 6.13 ± 0.46 | 2.81 ± 0.19 | 4.70 ± 0.71 | 2.37 ± 0.26 |
| Thyroid gland | 3.55 ± 1.03 | 6.89 ± 1.75 | 2.92 ± 1.09 | 18.14 ± 11.88 |
| Eye | 1.42 ± 0.34 | 15.86 ± 3.33 | 0.88 ± 0.26 | 18.48 ± 5.13 |
| Spleen | 0.58 ± 0.06 | 30.21 ± 2.46 | 0.28** ± 0.07 | 63.18 ± 18.09 |
| Liver | 0.40 ± 0.90 | 54.64 ± 12.78 | 0.32 ± 0.09 | 46.00 ± 11.92 |
| Gastric mucosa | 0.22 ± 0.11 | 211.69 ± 77.47 | 0.06 ± 0.01 | 546.01 ± 378.56 |
| Testis | 0.18 ± 0.03 | 177.49 ± 95.69 | 0.17 ± 0.02 | 64.44 ± 8.03 |
| Gastric muscle | 0.16 ± 0.01 | 105.80 ± 7.49 | 0.10* ± 0.02 | 130.19 ± 17.76 |
| Pancreas | 0.13 ± 0.04 | 213.9 ± 69.10 | 0.08 ± 0.04 | 279.86 ± 67.29 |
| Facial skin | 0.10 ± 0.03 | 240.27 ± 60.74 | 0.05* ± 0.01 | 218.00 ± 29.05 |
| Abdominal skin | 0.10 ± 0.02 | 200.78 ± 34.50 | 0.01*** ± 0.00 | 1281.10**± 275.26 |

Tissue blood flow (g $min^{-1}$ $g^{-1}$ tissue) and vascular resistance (VRU) in control animals (n=6) and animals pre-treated with nimodipine (n=8). Organs showing an increased blood flow after nimodipine pre-treatment are in the upper part of the Table. *p<0.05, **p<0.01, ***p<0.001 control vs. nimodipine group, unpaired Student's t-test.

tically significant decreased blood flow was observed due to vasoconstriction after nimodipine pre-treatment.

In Fig. 1a–d the relative change in blood flow and vascular resistance 5 minutes after soman intoxication in control and nimodipine pre-treated animals are presented.

In control rats, soman induced a significant increase in blood flow in the eye ($p<0.05$) and a significant decrease in the abdominal skin ($p<0.05$) 5 minutes after soman exposure (Fig. 1a and b). The vascular resistance was significantly decreased in the eye ($p<0.01$) and myocardium ($p<0.05$) while it was significantly increased in the kidney cortex, spleen and abdominal skin ($p<0.05$) (Fig. 1c and 1d).

In nimodipine pre-treated animals, soman significantly increased the blood flow in the tongue, eye, diaphragm ($p<0.05$), adrenal glands and myocardium ($p<0.01$) (Fig. 1a) concomitant with a decrease in vascular resistance, which was statistically significant except in the diaphragm and adrenal glands (Fig. 1c). In the pancreas ($p<0.05$), facial skin, jejunum, ileum, masseter ($p<0.01$), spleen and gastric muscle ($p<0.001$) (Fig. 1a and b), soman caused a statistically significant decrease in blood flow with an increase in vascular resistance. This increase was statistically significant except in pancreas and gastric muscle (Fig. 1c and d).

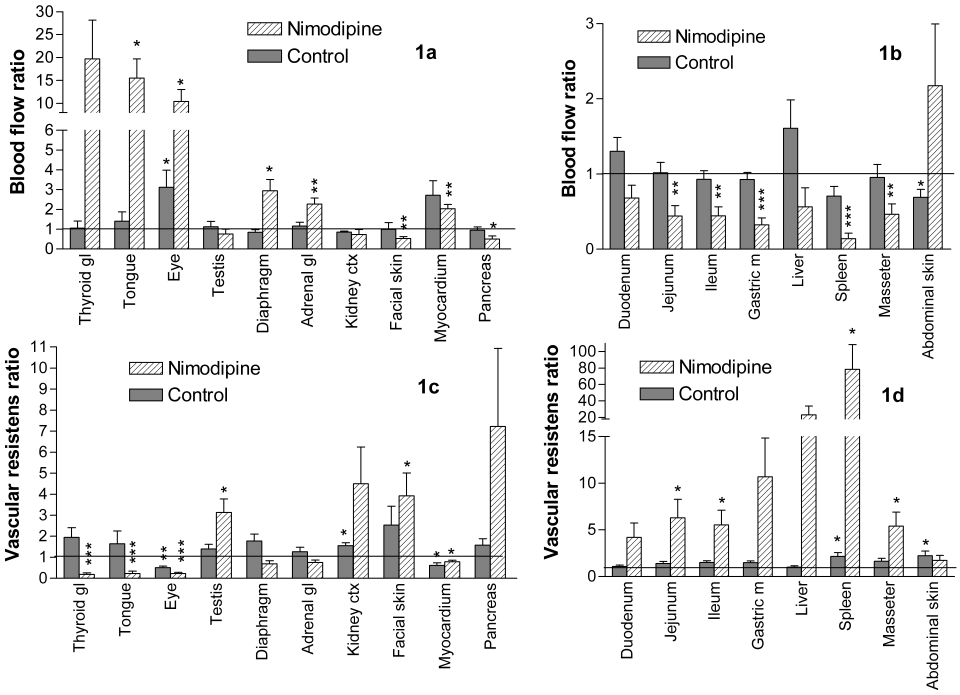


*Fig. 1a–d.* The relative changes in blood flow (a, b) and vascular resistance (c, d) 5 minutes after soman exposure in control (n=6) and nimodipine (n=8) pre-treated rats. The line represents the level of identity i.e. no change in blood flow or vascular resistance. *p<0.05, **p<0.01, ***p<0.001 paired Student's t-test.

## DISCUSSION

Nimodipine is a $Ca^{2+}$ antagonist that affects the L-type calcium channels in the cell membrane, especially in the smooth muscle. The smooth muscles in both cerebral and peripheral vessels are affected (11, 12). In a partially reversible focal cerebral ischemic rat model, intra-arterial injections of nimodipine reduced the infarct volume (20). Nimodipine is also clinically used to prevent and treat cerebrovasospasm in subarachnoid haemorrhage.

As soman is distributed through the body, the inhibition of acetylcholine esterase activates the cholinergic part of the nervous system. At the same time, soman is exposed to fast detoxifying processes, where the main processes are hydrolysis and binding to different esterases (8). Different organs contain different amounts of soman binding proteins and soman hydrolysing enzymes. Large amounts of available binding protein results in a faster soman disappearance from the blood. Blood flow through organs with binding capability is one of the more important factors that affect the soman detoxification (21). In our previous study (9) the detoxification of soman from rabbit blood was significantly increased during the first minute after administration in nimodipine pre-treated animals. One can speculate that the

blood flow changes elicited by nimodipine increase the aviability of soman detoxifying processes.

In the present study, soman exposure in nimodipine pre-treated rats induced vasodilation in tongue, eye, diaphragm, adrenal glands and myocardium. We also found that soman per se caused a significant vasoconstriction in the abdominal skin. This vasoconstriction was no longer evident after nimodipine pre-treatment. Thus, more blood is passing through the tongue, diaphragm and abdominal skin after soman intoxication in nimodipine pre-treated rats than in the controls. According to Langenberg *et al.* (8) the liver has the most and the kidneys the second most efficient soman binding capacity per gram tissue. In the present study no significant interaction of soman and nimodipine on the blood flow in the kidney cortex and the liver was detected. In a resting man, 20 % of the cardiac output perfuse the kidneys with a maximum blood flow around 1 l $min^{-1}$ (22). For comparison, the blood flow through the intestinal and hepatic artery at maximum dilation is about 2.5 l $min^{-1}$ for each, and through the skin around 3 l $min^{-1}$ in a 70 kg man. It should therefore be possible to expand the capillary bed in order to increase the availability of detoxifying enzymes. Nimodipine *per se* induces a vasodilation in the intestinal parts, muscles as diaphragm, myocardium, masseter and bisceps. Also in the liver nimodipine induces a slight vasodilation. These vasodilations may all contribute to an increased detoxification process during the first passage in nimodipine pre-treated animals.

Maxwell *et al.* (21) showed that the highest cholinesterase activity among peripheral organs was in the intestine, which also had the highest carboxylesterase activity. In the present study, no changes in the blood flow of the intestine could be detected after soman exposure in control animals. However, in nimodipine pre-treated animals soman induced a significant vasoconstriction in the jejunum, ileum and gastric muscle as the blood flow was significantly reduced and the vascular resistance significantly increased in jejunum and ileum. In the duodenum and gastric muscle, the vascular resistance was also increased but not significantly. In the spleen of control animals, the vascular resistance was significantly increased while the blood flow remained unchanged. This indicates that soman induces a slight vasoconstriction that is augmented by nimodipine pre-treatment since the blood flow significantly decreases. Kadar *et al.* (23) showed that soman was persistently bound to the lung and skin in mice. The specific binding capacity for soman in the skin is not very high. However, the skin is the largest organ with a significant vascular bed and its contribution should not be overlooked. Langenberg *et al.* (8) also points out the relative importance of the muscles and carcass (which include the skin) during the elimination phase, because of their volume. Moreover, during the early phase of intoxication the subcutaneous adipose tissue may function as a soman depot since it is lipid soluble (24). A slight vasoconstriction in the diaphragm of control rats became a significant vasodilation by nimodipine pre-treatment. This could contribute to the increased detoxification capability.

In summary, soman intoxication induces a significant vasoconstriction in the

abdominal skin, where the blood flow increases after nimodipine pre-treatment. In the eye, soman intoxication induces a slight vasodilation, which is even more pronounced after nimodipine pre-treatment. The non-significant increase in vascular resistance in the diaphragm of soman intoxicated rats, indicating a slight vasoconstriction, turns into a significant vasodilation by nimodipine pre-treatment. In the intestinal parts, no changes in blood flow or vascular resistance is seen after soman exposure while soman induces a significant vasoconstriction after nimodipine pre-treatment. Nimodipine *per se* induces a clear vasodilation in several tissues including some intestianl parts, myocardium and other muscles. Thus, one can speculate that a larger area for detoxification is available after nimodipine pre-treatment and this contributes to the incerased detoxification capacity the first minutes after intoxication. A more clinically oriented question to be answered is whether nimodipine treatment during muscle relaxation used during surgery, induces an increased need of AChE inhibitor during the finishing of muscle relaxation.

These results support our theory that nimodipine alters the peripheral blood flow in a beneficial way that improves the detoxification ability of soman.

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