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Neuropathy target esterase inhibitors – Evaluation of study results in biological material

Assessment Values in Biological Material – Translation of the German version from 2021

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated the inhibition of neuropathy target esterase (NTE). A biological tolerance value (BAT value) could not be derived due to insufficient data.

It has been proposed that the inhibition of NTE by organophosphorylation prevents the maintenance of axonal integrity leading to a central–peripheral distal axonopathy of long sensorimotor axons in peripheral nerves and spinal cord. Neuropathic organophosphates are known to produce this disease, called organophosphate-induced delayed neuropathy (OPIDN). The few available studies on the relationship between external and internal exposure to neuropathic organophosphates and inhibition of NTE are described and a compilation of literature data on the degree of NTE inhibition and the occurrence of OPIDN is presented. In addition, the available literature on NTE activity at background exposure is summarized.

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BAT (2020) **not established**

1 Biochemical Facts/Pathomechanism

Single or repeated exposure to organophosphates with specific chemical properties (neuropathic organophosphates) can lead to peripheral neuropathy, the morphological correlate of which is axonal degeneration of sensory and motor neurons in the spinal cord and peripheral nervous system (Glynn 1999). This delayed neurotoxicity, which occurs one to four weeks after exposure and displays symptoms of ataxia and spasticity, is known as OPIDN (organophosphate-induced delayed neuropathy) (Abou-Donia 2003; Lotti and Moretto 2005; Richardson et al. 2013). The inhibition of neuropathy target esterase (NTE), a serine hydrolase, by phosphorylation of serine in the active centre is discussed as a possible cause (Glynn 1999; Johnson 1969). According to the current hypothesis, neuropathic organophosphates bind to serine to form a seryl ester. An alkyl group can split off from this ester, leaving a negatively charged phosphoryl residue in the active centre of the esterase. This irreversible step is known as "ageing" and appears to play a causal role in the formation of OPIDN (Richardson et al. 2013). Mechanistic studies have shown that the inhibition of other esterases, such as acetylcholinesterase or butyrylcholinesterase, is not causally involved in the development of OPIDN (Abou-Donia 2003).

OPIDN is induced only by organophosphates that trigger the "ageing" process (= neuropathic organophosphates), while non-neuropathic organophosphates inhibit NTE but do not cause "ageing" or neuropathy. Animals pretreated with non-neuropathic organophosphates are protected against OPIDN if subsequently exposed to neuropathic organophosphates (Johnson et al. 1988; Johnson and Read 1993).

Structure–activity relationships indicate structural differences between these two groups (Johnson 1988; Richardson et al. 2013).

Sufficient inhibition of the NTE in the first one or two days after exposure can later lead to OPIDN. The enzyme itself has a regeneration half-life of five to seven days and its activity has already returned to normal by the time clinical symptoms occur (Richardson et al. 2013).

2 Critical Toxicity

OPIDN is a relatively rare neurodegenerative disease. The first neurological symptoms are usually cramp-like pain in the calves, tingling in the feet, followed by distal numbness and paraesthesia (Lotti et al. 1984). Progressive muscle weakness then develops with depression of reflexes and ataxia. Pain and weakness in muscles spread rapidly and affect mainly the lower limbs. The muscle tonus of the limbs gradually increases and spasticity might later appear in the lower limbs mainly in severe cases (Jokanović et al. 2011).

The cause is believed to be a malfunction of the NTE protein encoded by the patatin-like phospholipase domain containing 6 (PNPLA6) gene (NCBI GeneID 10908; aliases NTE, SPG39). NTE is present mainly in nerve membranes and lymphocytes and plays a role in phospholipid homoeostasis of the endoplasmic reticulum (ER) (Dudek and Richardson 1982; Richardson et al. 2013). A dysfunction of the ER inhibits axonal transport and impairs the interaction between axon and glial cells (Glynn 2007). A deletion of NTE in adult mouse brain leads to dysfunction of the ER and to morphological changes in neurons (Akassoglou et al. 2004). Mutations in the NTE gene are also associated with diseases of the motor neurons (Rainier et al. 2008). These observations seem to support the hypothesis that genetically or chemically modified NTE leads to axonal degeneration.

It is postulated that the so-called "fume events" (events in aircrafts where potentially contaminated bleed air enters the cabin) lead to a reduction in NTE (Heutelbeck et al. 2016).

3 Exposure and Effects

There are hardly any studies on the relationship between external and internal exposure to neuropathic organophosphates and exposure in the form of inhibition of NTE (see Table 1). Animal studies have investigated the decrease in NTE activity leading to OPIDN. In two case studies, the activity of NTE after human exposure was related to neurological symptoms and to internal concentrations of neuropathic organophosphates (Lotti et al. 1986; Osterloh et al. 1983). The examination of members of an aircraft crew after a stated fume event was also reported (Heutelbeck et al. 2016).

3.1 Animal studies

Adult hens were initially considered to be an optimal model to study neuropathic organophosphates and their effect on NTE.

In two studies, hens were given a single oral gavage dose of diisopropyl fluorophosphate (1 mg/kg body weight) or treated for 40 days (125 µg/kg body weight and day) (Johnson and Lotti 1980; Olajos et al. 1978). The activity of NTE was studied in the brain of the animals 24 hours and 48 hours after the exposure. While a 12% decrease in activity was already associated with the occurrence of ataxia (Olajos et al. 1978), no symptoms in the same study protocol with a decrease in NTE activity by up to 60% was observed (Johnson and Lotti 1980).

In another study, hens were given oral doses of diphenyl cresyl phosphate of 2.5 mg/kg body weight daily for up to ten weeks. NTE activity in the brain and spinal cord fell to 40% to 55% without histological changes or neurological symptoms. A higher daily dose of 5 mg/kg body weight or a single dose of 50 mg/kg body weight resulted in a decrease in the NTE activity by > 80% and the appearance of neurological symptoms (Johnson and Lotti 1980).

Mice and rats do not show ataxia or paralysis, so they initially seemed unsuitable as models. However, since they develop axonal lesions after exposure to neuropathic organophosphates, they were used also for in vivo experiments.

Rats were given tri-o-cresyl phosphate in single oral doses of 145–3480 mg/kg body weight. The activity of the NTE was determined in the brain and spinal cord 20 hours and 44 hours after the exposure (Padilla and Veronesi 1985). Axonal changes in the spinal cord were histologically examined 14 days after the exposure. A decrease in NTE activity by 40% (spinal cord) and 36% (brain) resulted in severe neuronal lesions. It was not reported which activities of the NTE led to the first changes in axonal activity.

Winrow's group generated an $NTE^{+/-}$ mouse model with an NTE inhibition of about 40% in the brain (Winrow et al. 2003). In these animals, no differences in learning ability and memory were found compared with the wild type. However, the $NTE^{+/-}$ mice were more motorically active than the wild type. No clear differences in histological changes in brain and spinal cord were found between $NTE^{+/-}$ and wild type mice.

3.2 Human studies

There are two case reports in the literature:

A 26-year-old man ingested 360 ml of Dexol® (containing 6.7% chloropyrifos) and 360 ml of Ortho Weed-B-Gone M (containing 10.8% dimethylammonium 2,4-dichlorophenoxyacetate, 1.6% 2-(2-methyl-4-chlorophenoxy)propionic acid; 77.6% inert aqueous components) and a few granules of D-Con concentrate (0.025% warfarin). The patient was initially agitated and hostile and progressively became unresponsive, tachycardic (150 beats/min), hypertensive (170/110 mmHg), showed myoclonus and miotic-reactive pupils. Reflexes were normal. Initial electrocardiograms showed prolongation of the QT interval, peaked T waves, and sinus tachycardia. Diarrhoea, further cardiac arrhythmias, hypotension and acidosis occurred later. The patient died after 30 hours. Toxicological parameters measured included the concentrations of dichlorophenoxyacetic acid, 2-(2-methyl-4-chlorophenoxy)propionic acid and chlorpyrifos at various times after ingestion in blood and 16 hours post mortem in various tissues. Activities of acetylcholinesterase, butyrylcholinesterase (both measured in erythrocytes, plasma and post-mortem tissue) and NTE (in brain, spinal cord and lymphocytes)

were determined immediately after ingestion and 13, 19, 26, and 30 hours post-mortem. Acetyl and butyrylcholinesterase activities in erythrocytes were normal or slightly inhibited immediately after ingestion and decreased or were no longer measurable during the rest of the observation period. Lymphocytic NTE activity was initially normal, then dropped to 50% after 14 hours and returned to normal. The patient showed minimal cholinergic symptoms or minimal symptoms of intoxication with neuropathic organophosphates. Ataxia or paralysis of the lower extremities were not observed (Osterloh et al. 1983).

In a second case report, a 42-year-old man drank about 30 mg/kg body weight of chlorpyrifos with suicidal intent. The man was initially asymptomatic and was admitted comatose and with respiratory insufficiency to the hospital 18 hours after ingestion. He showed classic muscarinergic and nicotinergic symptoms (lacrimation, salivation, sweating, bronchial hypersecretion, miosis and fasciculations), which subsided until the 24th day after ingestion. OPIDN symptoms (weakness and paraesthesia in the legs with reduced tendon reflex) began on day 43. The patients' symptoms developed progressively. Biopsies showed degenerative changes in the axons on day 63. In contrast to the animal experiments, polyneuropathy occurred only after six weeks, which the authors explained by the slow elimination of the high dose of chlorpyrifos, which may also explain the pronounced inhibition of esterases four weeks after ingestion. The lymphocytic NTE inhibition four weeks after ingestion was 60%, earlier measurements were not possible (Lotti et al. 1986).

Another study examined 11 cabin crew members of an aircraft five days after a reported fume event. Exposure to NTE inhibitors could not be verified. The clinical examination revealed symptoms of cholinergic intoxication as well as signs of peripheral and central nervous disorders. In 10 patients, the NTE activity was between 3.14 and 6.3 nmol phenylvalerate/(min × mg protein) and, in one patient, 1.4 nmol phenylvalerate/(min × mg protein). Inhibition of the NTE activity was not determined (Heutelbeck et al. 2016).

Tab. 1 Relationship between NTE activity and OPIDN

Species	NTE inhibition [%]	NTE activity [nmol/min/mg protein]	Symptoms/histology	References
hen	12 (brain)	control: 13.78 ± 0.66 µg/ml at 12% inhibition: 12.2 ± 0.28 µg/ml	ataxia	Olajos et al. 1978
hen	63 (brain)	–	–	Lotti and Johnson 1980
rat	36 (brain)	control: 7.83 ± 0.17	wider and more lateral band of degeneration noted along the fasciculus	Padilla and Veronesi 1985
NTE$^{+/-}$ mice	40 (brain)	–	hyperreactivity; no clear histological changes	Winrow et al. 2003
human (n = 1)	50 (lymphocytes) 14 hours after ingestion with chlorpyrifos, dichlorophenoxyacetic acid and 2-(2-methyl-4-chlorophenoxy)propionic acid	(control) value (immediately after ingestion): ~11.5[a)] 14 hours after ingestion: ~6.2[a)]	miosis, no ataxia, no paralysis, †	Osterloh et al. 1983
human (n = 1)	60 (lymphocytes) 28 days after ingestion of chlorpyrifos	(control) value (90 days after ingestion): ~ 13.5[a)] 28 days after ingestion: ~ 6[a)]	ataxia, paralysis, degenerative axonal changes	Lotti et al. 1986

[a)] read from figure

4 Selection of the Indicators

According to the current state of knowledge, the determination of NTE inhibition covers the effect parameter that is biologically relevant to the damage, independent of the chemical structure of the NTE inhibitor. It turned out that the determination of the reduction of the activity of the NTE in lymphocytes is particularly suitable for quantitative statements in terms of biomonitoring (Bertoncin et al. 1985; Dudek and Richardson 1982; Lotti et al. 1986; see also Lewalter et al. 2008).

5 Methods

In most of the available publications, a method essentially described by Johnson (1977) is used to determine the activity of the NTE. This was also the basis for the analytical method validated and published by the working group "Biomonitoring" (Lewalter et al. 2008), which can be used to determine the activity of NTE in isolated leukocytes. The determination is based on the enzymatic cleavage of the substrate phenylvalerate to phenol, which can be determined photometrically at 492 nm using a colour reaction. In the studies of Sigolaeva et al. (2001, 2013) on the other hand, a biosensor method was used.

6 Background exposure

The activity of the NTE without exposure to neuropathic organophosphates has been determined in only a few studies (see Table 2 and Figure 1). The NTE activity was determined in lymphocytes in a study with 108 men and women. The mean value of these measurements was 11.5 ± 2.5 nmol phenylvalerate/(min × mg protein). No gender-related or age-related differences were found. The intraindividual variation of NTE activity in lymphocytes was investigated in seven subjects over a period of 0 up to more than 210 days. The averaged coefficient of variation was 10.1% (Bertoncin et al. 1985).

The NTE activity in lymphocytes of 68 non-exposed subjects was 13.34 ± 2.42 nmol phenylvalerate/(min × mg protein) and smoking had no effect on the NTE activity (Maroni and Bleecker 1986).

The NTE activity was also investigated in lymphocytes from blood samples of 137 healthy employees of a company. Here the NTE activities were between 3.7 and 21.8 nmol phenylvalerate/(min × mg protein). The arithmetic mean value was 8.1 ± 3.0 nmol phenylvalerate/(min × mg protein). Initial determinations in blood samples of five healthy, non-exposed volunteers revealed NTE activities of 3.8 to 7.7 nmol phenylvalerate/(min × mg protein) (Ruhnau et al. 2001).

A Japanese study investigated the NTE activity in 52 healthy, non-exposed people. The mean value was 0.54 ± 0.22 nmol/min/10^6 lymphocytes. As the conversion to protein content is problematic, this study was not included in Table 2 (Matsuzaka et al. 2014).

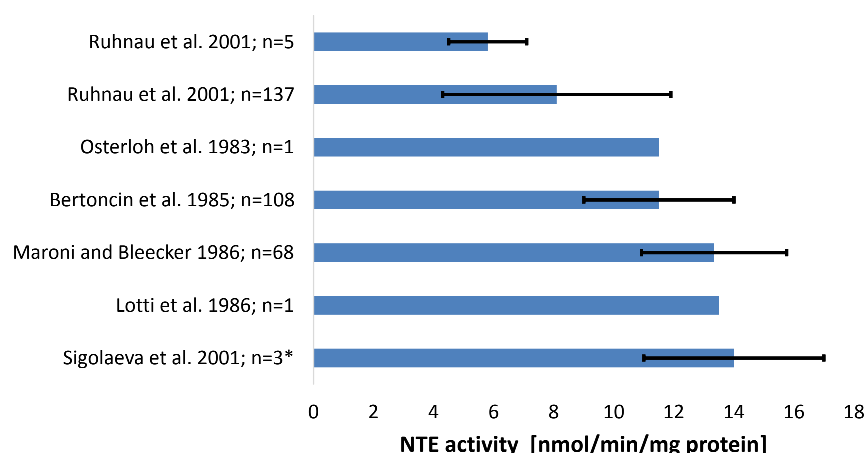
An NTE activity of 14 ± 3 nmol phenylvalerate/(min × mg protein) in lymphocytes of three healthy persons was determined using a biosensor method. A value of 15.3 ± 2.32 nmol phenylvalerate/(min × mg protein) was obtained in the whole blood of four persons (Sigolaeva et al. 2013). As whole blood was used as biological material for the latter study, these results were not included in Table 2.

As described above, there are, in addition, two case studies on chlorpyrifos intoxication. In both cases, NTE activities were determined, which were regarded as control values by the authors. They were 11.5 and 13.5 nmol phenylvalerate/(min × mg protein), respectively, and are thus in the range of the values already described (Lotti et al. 1986; Osterloh et al. 1983).

Tab. 2 Overview of NTE activity in lymphocytes of persons not exposed to neuropathic organophosphates

Collective, n, NTE activity	References
(Caucasian, n = 108) mean 11.5 ± 2.5 nmol phenylvalerate/(min × mg protein)[a)] mean intraindividual coefficient of variation: 10.1%, no gender-related or age-related differences	Bertoncin et al. 1985
(n = 68) mean 13.34 ± 2.42 nmol phenylvalerate/(min × mg protein)[a)]	Maroni and Bleecker 1986
(laboratory staff; n = 5) range 3.8–7.7 nmol phenylvalerate/(min × mg protein)[a)] mean 5.8 ± 1.3 nmol phenylvalerate/(min × mg protein)[a)] (n = 137) range 3.7–21.8 nmol phenylvalerate/(min × mg protein)[a)] mean 8.1 ± 3.0 nmol phenylvalerate/(min × mg protein)[a)] median 7.8 nmol phenylvalerate/(min × mg protein) [a)]	Ruhnau et al. 2001
(n = 3) mean 14 ± 3 nmol phenylvalerate/(min × mg protein)[b)]	Sigolaeva et al. 2001

[a)] method based on Johnson (1977) and validated extensively by Lewalter et al. (2008); [b)] biosensor method (Sigolaeva et al. 2001)



* biosensor method (Sigolaeva et al. 2001)

Fig. 1 Mean values and standard deviations of the NTE activity in lymphocytes

7 Evaluation of the BAT Value

Summarising the available studies with regard to the possibility of deriving a biological tolerance value (BAT value), humans and mammals appear to be more sensitive to inhibition of NTE by neuropathic organophosphates than hens. A 40% decrease in activity resulted in neurological symptoms and histological changes in rats and mice. In humans, in one case of poisoning with a neuropathic organophosphate, a 60% inhibition of the NTE activity led to initial neurological symptoms, while in another case of poisoning, a 50% inhibition of the NTE activity was associated with lethality. Overall, the data are insufficient, as only a few publications are available, and

it is not possible to derive a BAT value based on the inhibition of the neuropathy target esterase activity in lymphocytes.

8 Interpretation

Due to the intraindividual range of variation in NTE activity, only the difference from the initial activity allows possible conclusions to be drawn (i. e. inhibition of the activity of NTE). **Pre**-exposure values for exposed workers must therefore be determined as part of occupational health surveillance. Sampling **after** exposure shall be carried out at the end of exposure or end of shift, in case of long-term exposures: at the end of the shift after several previous shifts.

NTE is inhibited only by some (neuropathic) organophosphates. In order to evaluate the handling of organophosphates as a whole, the activity of acetylcholinesterase should therefore be determined in each case.

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