Nitric oxide production and monoamine oxidase activity in cancer patients during interferon-\(\alpha\) therapy

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Received: 28 August 2008 / Accepted: 5 October 2008 / Published online: 26 October 2008 © The Author(s) 2008. This article is published with open access at Springerlink.com

Abstract Both increased and decreased nitric oxide (NO) synthesis have been reported in patients treated with interferon-\(\alpha\) (IFN-\(\alpha\)). Animal studies showed that IFN-\(\alpha\) administration results in increased levels of biogenic amines, subsequent activation of monoamine oxidases (MAOs), and finally in a change in NO production due to the \(H_2O_2\) generated by MAOs. We examined the potential relationship between NO production in plasma and MAO-B activity in platelets of 43 cancer patients during 8 weeks of treatment with IFN-\(\alpha\). NO synthesis was quantitated by measuring both the ratio of citrulline and arginine (CIT/ARG-ratio) and total nitrite/nitrate (NOx) levels. Compared to baseline, MAO activity and NOx increased, while the CIT/ARG-ratio decreased. No associations were found between NOx, MAO and CIT/ARG-ratio. Only few associations were observed between changes in the biochemical parameters and changes in psychopathology induced by IFN-\(\alpha\), of which the association between changes in CIT and lassitude was the most consistent. The results suggest that peripheral NO production and MAO activity are unrelated to each other, and that peripheral changes in these biochemical parameters induced by IFN-\(\alpha\) are unlikely to contribute to definite psychiatric disturbance.

Keywords Citrulline · Depression · Interferon-\(\alpha\) · Nitric oxide · Monoamine oxidase · Cancer

Introduction

Treatment with the cytokine interferon-\(\alpha\) (IFN-\(\alpha\)) is associated with the development of psychiatric side effects, most notably depression (Fekkes and Van Gool 2003). Many pathways and mechanisms have been proposed that could potentially mediate the neuropsychiatric side effects of cytokine therapy, e.g., derangements in serotonergic (Bonaccorso et al. 2002) and the nitric oxide (NO) systems (Bogdan 2001). The latter system has also been hypothesized to be involved in depression (Van Amsterdam and Opperhuizen 1999; Hurlock 2001), which is substantiated by the findings that the antidepressant paroxetine inhibits NO synthesis (Goodnick and Goldstein 1998) and that nitric

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oxides (NOS) inhibitors display antidepressant-like properties in animal models (Harkin et al. 1999). Although pro-inflammatory cytokines are known to induce the expression of inducible NOS (iNOS), conflicting results have been reported regarding the effect of the cytokine IFN-γ on the in vivo production of NO. Using plasma nitrite/nitrate concentrations as a measure of NO production, an increase of nitrate levels was found in chronic hepatitis C patients who developed depression in the first 4 weeks of treatment with IFN-γ. No change in plasma nitrate was seen in patients on IFN-γ without depressive symptoms and in patients who developed a depression later in the course of treatment with IFN-γ (Suzuki et al. 2003). In contrast, we found a decrease in NO synthesis in patients with high risk melanoma treated with pegylated IFN-γ, applying the plasma concentration of the amino acid citrulline (CIT) and the ratio of CIT to arginine (ARG; CIT/ARG-ratio) as indices of NOS activity (Fekkes et al. 2007). Another study, in which rats were chronically injected with IFN-γ during a period of 14 days, failed to show any change in the brain content of nitrite/nitrate (Sato et al. 2006).

In addition, to having an effect on the NO system, IFN-γ may also influence the activity of several enzymes, such as indoleamine 2,3-dioxygenase (IDO) and monoamine oxidases (MAOs). IFN-γ stimulates the expression and activity of the enzyme IDO, which converts tryptophan into kynurenine. Kynurenine is further metabolized into several neuroactive metabolites, of which 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid can generate reactive oxygen species (ROS), such as H₂O₂ (Wichers and Maes 2004). The reactive molecule H₂O₂ may also be formed during the oxidative deamination of primary amines catalyzed by MAOs, which are flavoproteins located in the mitochondrial outer membrane (Pizzinat et al. 1999). Animal studies showed that IFN-γ administration results in increased levels of catecholamines in cerebral cortex and hypothalamus of rats (Kumai et al. 2000). Studies with peritoneal macrophages suggested that an increased production of biogenic amines observed during inflammatory processes may subsequently result in activation of MAOs (Vega et al. 2004). The latter group also found that the H₂O₂ generated by MAOs inhibited NO production and iNOS expression. In contrast, other investigators found the opposite and reported that H₂O₂ enhanced iNOS expression and NO production in peritoneal macrophages when interferon-γ was added, but that the produced NO was in turn a negative feedback inhibitor of iNOS protein expression (Han et al. 2001). Collectively, it remains unclear whether MAO activation impacts NO production, and if so, to which direction.

In a previous study we found increased MAO-B activity in platelets of patients with high risk melanoma undergoing IFN-γ treatment (Bannink et al. 2005). However, in this study as well as in the earlier mentioned one on NO (Fekkes et al. 2007), no psychiatric measurements were conducted, and therefore we could not correlate the changes in MAO activity and NO production to psychopathology. This prompted us, to reinvestigate the influence of treatment with IFN-γ on these biochemical parameters in another group of oncology patients to test our hypothesis (Fekkes et al. 2007) with particular reference to psychiatric ratings. After the study was initiated, study recruitment of patients with high risk melanoma ended and at the same time another trial with patients having disseminated renal cell carcinoma was initiated. Since we wanted to examine the effects of IFN-γ on the abovementioned parameters, we decided to combine both patient groups for this study. Recently, the results of the psychiatric assessments of this patient cohort, which were performed at regular time points in the first 6 months of treatment, have been published by our group and the outcomes of the first 8 weeks of treatment with IFN-γ are used in this study (Bannink et al. 2008).

The aims of the present prospective study are (1) to investigate again the CIT/ARG-ratio in plasma and platelet MAO-B activity in another group of oncology patients, (2) to measure the total concentration of nitrite and nitrate (NOx) as an index of NO synthesis, (3) to relate the measurements of CIT/ARG-ratio to NOx and to MAO-B activity in order to answer the question whether the expected increased MAO activity results in a decreased or an increased formation of NO, and (4) to test the hypothesis whether changes in the biochemical parameters show any correlation with changes in psychiatric ratings.

Materials and methods

Patients and psychiatric assessments

Demographic data of the patients, data on the oncological treatment and on methods of assessment of psychiatric symptoms and syndromes, are reported in detail elsewhere (Bannink et al. 2008). In brief, 43 patients, 25 men and 18 women, age 36–72 years (median 58 years) were recruited to the study. Eight high risk melanoma patients participated using pegylated (PEG) IFN-γ 6 μg/kg per week s.c. for a period of 8 weeks. Thirty-five patients with disseminated renal cell carcinoma (RCC) were given IFN-γ s.c., initially in a dose of 3 MU, 3 times a week, escalating within 4 weeks to 9 MU s.c. 3 times a week.

For this study, results of psychiatric assessments at baseline, and at 4 and 8 weeks after the start of IFN-γ treatment were used. The following measures for psychiatric disorder were selected: the Montgomery–Asberg Depression Rating Scale (MADRS), the item on hostility of
the Brief Anxiety Scale (BAS) and the Symptom Check List-90 (SCL-90), which scales are all described in more
detail in the afore-mentioned study (Bannink et al. 2008).
All patients gave written informed consent, and the study
was approved by the Medical Ethics Committee of the
Erasmus MC and was carried out in accordance with the
declaration of Helsinki.

Laboratory assessments

EDTA blood was obtained by venipuncture at the same
time as the psychiatric assessments were performed. For
practical reasons, it was not possible to obtain blood
samples at fixed times or under fasting conditions. A 1-ml
blood sample was frozen at −80 °C for determination of
MAO activity as previously described and expressed as
μmol of 4-hydroxyquinoline formed per 10^9 platelets per
hour (Bannink et al. 2005). The remainder was centrifuged
for 20 min at 2,650gmax and 20 °C, and plasma was
frozen at −80 °C. Amino acids were determined as previ-
ously described (Fekkes et al. 1995). Of the last 14
consecutive participants, of whom both blood samples
could be obtained and all psychiatric evaluations were
performed, NO was determined by measuring plasma
nitrite + nitrate by the Griess reaction after conversion of
nitrate to nitrite using a commercially available assay kit
(R&D Systems, Abingdon, UK). Patients from this sub-
group were all diagnosed with RCC and treated with
standard IFN-α.

Statistical analysis

Data were stored and analyzed using SPSS software, ver-
sion 10.0. Outcomes at 4 and 8 weeks were compared to
those at baseline using the Wilcoxon matched-pairs signed-
rank test. The Spearman rank correlation test was used to
evaluate the correlation between laboratory parameters and
psychiatric ratings, and to evaluate the changes in all
parameters at both time points compared to baseline. The
Spearman rank correlation coefficient (rho) and the corre-
sponding P value were calculated for all paired
observations and pairs of changes. In addition, a repeated
measures ANOVA was performed incorporating only those
subjects of whom both laboratory parameters and psychi-
atriac ratings were available at all three time points. All
reported P values are two-sided and a significance level
α = 0.05 was used.

Results

Of the 43 patients recruited, 40 blood samples could be
assessed at baseline; data were missing from 3 patients due
to administrative failure. At the other evaluation times,
samples and data of 9 (4 weeks) and 12 (8 weeks) patients
were missing due to disease progression and cessation of
treatment because of severe side effects, or due to problems
unrelated to side effects. The concentrations of CIT and the
CIT/ARG-ratio were significantly decreased at both time
points during treatment compared to baseline (Table 1).
The ARG concentrations showed no significant changes.
Platelet MAO activity was significantly increased at both
time points compared to baseline. The NOx concentrations
in the subgroup of 14 patients were increased at 4 and
8 weeks after starting treatment. Essentially, the same
results were obtained after employing a repeated measures
ANOVA on the remaining 31 patients of whom all data
were present, except for the change in NOx levels at
4 weeks, which was not significantly different from base-
line (P = 0.11).

No statistically significant correlations were observed
between the change compared to baseline of NOx levels
and the change compared to baseline of the CIT/ARG-ratio
at 4 weeks (Spearman’s rho, −0.21; P = 0.47) and
8 weeks (Spearman’s rho, −0.17; P = 0.56). In addition,
no significant correlations were observed between the
change compared to baseline of platelet MAO activity and
the change compared to baseline of the CIT/ARG-ratio at
4 weeks (Spearman’s rho, −0.12; P = 0.50) and 8 weeks
(Spearman’s rho, −0.18; P = 0.38), as well as between the
change compared to baseline of platelet MAO activity and
the change compared to baseline of the NOx levels at
4 weeks (Spearman’s rho, 0.52; P = 0.07) and 8 weeks
(Spearman’s rho, 0.30; P = 0.32).

The observed significant correlations (P < 0.05) be-
tween changes in selected items of observer based and
self-report rating scales compared to baseline and changes
in laboratory parameters compared to baseline are sum-
marized in Table 2. Changes in the concentrations of CIT
were correlated to changes in the score on the subscale on
somatic complaints of the SCL-90 at 8 weeks (P = 0.04),
and on both time points to changes on the MADRS item on
lassitude (P = 0.02 in both instances). At 4 weeks after the
start of treatment, changes in ARG concentrations were
related to changes in the sumscore of the SCL-90
(P = 0.02) and in the scores on three SCL-90 subscales,
i.e., depression (P = 0.05), anxiety (P = 0.05), and
somatic complaints (P = 0.01). At 8 weeks, changes in
ARG concentrations were related to changes in the sub-
scale hostility of the SCL-90 (P = 0.05). Most notably, no
correlations at all were observed between changes in the
CIT/ARG-ratio and changes in psychiatric measures.
Changes in platelet MAO activity were only correlated to
changes on the SCL-90 subscale somatic complaints at
8 weeks (P = 0.05). In the subgroup of 14 patients of
which NOx concentrations were determined, only a
A correlation was observed between change in NOx concentrations and change in the hostility subscale of the SCL-90 at 8 weeks ($P = 0.03$).

### Discussion

In this study, we could confirm our previous findings that IFN-α treatment resulted in (1) a consistent increase in the platelet MAO activity, and (2) a consistent decrease in plasma concentrations of the amino acid CIT and of the CIT/ARG-ratio. Although this decrease of the CIT/ARG-ratio is suggestive of an overall decrease of NOS activity during treatment with IFN-α, the opposite is suggested by the observed increase of the concentration of NOx. Furthermore, no correlation was observed between the changes of the two putative indices of NO production used in this study compared to baseline during treatment with IFN-α.
although the number of patients involved is rather small to
draw firm conclusions. There were also no correlations
between changes in MAO-B activity and changes in CIT/
ARG-ratio on the one hand and changes in NOx levels on
the other hand. Therefore, the question whether the
increased MAO activity results in a decreased or an
increased formation of NO cannot be answered. Finally,
our hypothesis whether changes in the biochemical
parameters show any correlation with changes in psychi-
atric ratings was tested. It appeared that only in a few
instances changes in the biochemical parameters correlated
significantly with changes in psychiatric ratings, and that of
these associations, only the correlations between changes
in CIT levels to changes in the scores on the lassitude item
of the MADRS seemed consistent, since these were sig-
nificant (P = 0.02) both after 4 and 8 weeks of IFN-α
treatment. However, after all this result is not so surprising,
since no definite clinically relevant IFN-α induced psy-
chiatric side effects were observed in this patient cohort
(Bannink et al. 2008).

Platelet MAO activity has been proposed to serve as a
marker for brain MAO and may also reflect central sero-
tonergic capacity and/or turnover (Stahl 1985; Oreland and
Hallman 1995). We validated the original increase in
MAO-B activity in platelets of patients treated with the
pro-inflammatory cytokine IFN-α in a larger patient sample
(Bannink et al. 2005). Our results are in line with those of a
previous study, which reported that inflammatory processes
may result in activation of MAOs (Vega et al. 2004).
Although the latter group found that the H2O2 generated by
MAOs inhibits NO production, we did not find a significant
correlation between the increase in MAO-B activity and the
decrease in NO production using the CIT/ARG-ratio as an
index of NO synthesis. If we use NOx measurement as a
reflection of NO production, we found that the increase in
this parameter is accompanied by an increase in MAO-B
activity, which is in line with the enhanced NO production
found in peritoneal macrophages after the addition of interferon-γ and H2O2 (Han et al. 2001). However, again no
significant correlation was present between changes in both
parameters in our study.

As already mentioned earlier and discussed in more
detail in a recent paper on the psychopathology of this
patient cohort (Bannink et al. 2008), we noticed only few
changes in psychiatric parameters during IFN-α-based
treatment. Therefore, the few and clinically not relevant
associations found between any changes in biochemical
parameters and changes in psychiatric ratings come as no
surprise. Although IFN-α treatment of our cohort of
oncology patients provoked many biochemical changes—
increase in platelet MAO activity and plasma NOx levels,
and a decrease in CIT/ARG-ratio in this study, as well as
an increased degradation of peripheral tryptophan and
enhanced plasma concentrations of the cellular immune
activation marker neopterin (Bannink et al. 2007)—these
alterations were not accompanied by the appearance of
clinically relevant psychiatric side effects, except for the
consistent and significant correlation between a decrease in
plasma levels of CIT and an increase in the item lassitude
of the MADRS during the whole period of IFN-α treat-
ment. Therefore, our results do not lend support for an
important role of a derangement in either MAO activity or
NO synthesis as a mechanism underlying IFN induced
psychopathology.

The results of our study do not answer the question
which of the two methods for assessing peripheral NO
production is the most valid one. On the one hand, one
could doubt the validity of the use of the amino acids CIT
and ARG as indices for NO production as the metabolism
of CIT and ARG is complex. This has already been dis-
cussed earlier (Fekkes et al. 2007). On the other hand, the
assay of NOx is fraught with technical difficulties and
blood concentrations of nitrite/nitrate are influenced by
factors as diet, physical activity and antioxidants taken
(Tsikas and Frölich 2004; Dusse et al. 2005). In order to
elucidate the best strategy to assess NO synthesis in the
circulation, we would recommend in future studies into the
role of NO metabolism in IFN-α-induced psychopathology
to measure both the CIT/ARG-ratio and NOx levels in
plasma, as done in the present study.

Some caution should be exercised when interpreting our
results. First, most reports on patients treated with IFN-α
mention considerably higher rates of psychopathology than
we observed in the population studied. Other factors, such
as the gradual increase of the dose of IFN-α in this study,
could have provided our patients with a resilience to the
psychotropic effects of IFN-α and could have counterbal-
canced effects resulting from changes in NO synthesis or
MAO activity. Second, our laboratory assessments were
performed in the peripheral compartment, whereas the
influence of NO on neurotransmission is thought to take
place on a cellular level in the brain. Possibly, the regu-
lation of NO synthesis may well vary between the different
compartments. It is also uncertain whether central MAO
activity is adequately reflected by platelet MAO activity.
Third, this research was performed in a mixed group of
oncology patients, comprising patients who were either
clinically disease-free or had disseminated disease and they
were treated with two types of IFN-α. One may speculate
that these differences might have influenced biochemical
and/or psychiatric outcome. Fourth, in this patient cohort of
modest size a large amount of parameters were investi-
gated, which may increase the risk of chance findings.

In conclusion, our study does not demonstrate an asso-
ciation between changes in NO production and changes in
MAO activity on the one hand, and changes in these
biochemical parameters and changes in psychiatric ratings on the other hand in cancer patients treated with IFN-α. Furthermore, despite great alterations in the parameters assessed thought to reflect MAO activity and NO synthesis, no definite psychiatric side effects were encountered rendering it unlikely that these factors are involved in IFN-α-induced mood alterations.

Acknowledgments This study was financially supported by a grant of the Foundation Nuts OHRA. The authors thank Ms. E. Bogaerts-Taal, Ms. S. A. van der Heide-Mulder, Ms. A. C. C. Voskuilen-Koosijman, Ms. M. Dros, Ms. A. van der Eng-Schipper, Ms. H. van der Eng, Ms. M. Mojka, Ms. C. H. C. van Noort, Ms. T. J. P. Pronk and Mr. H. van der Meulen for their skilled technical assistance.

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