Chapter 10
General discussion

This thesis is concerned with physiological causes and psychopa-
thological consequences of fluctuating tryptophan levels. This is
relevant because production of the pivotal neurotransmitter 5-HT
depends heavily on plasma tryptophan levels. Several conditions
with attenuated plasma tryptophan levels are described. In carcinoid
patients tryptophan levels are low because of peripheral consump-
tion of the amino acid by malignant cells in the gut. In these patients
we observed impulsive aggressive behavior and attenuated plasma
tryptophan levels in a substantial proportion of patients (chapter 3).
Furthermore, carcinoid patients also perform superior on a cognitive
task measuring rapid attention shift (chapter 4). Observations in die-
tary tryptophan depleted healthy volunteers of increased irritability
and vigilance closely resemble these findings (Schmitt et al. 2000,
Cleare et al. 2000). Those observations together are consistent with
the idea that the behavioral and cognitive observations in carcinoid
patients can indeed be attributed to low plasma tryptophan levels.
However, the association remained correlative rather than causal.
Furthermore, plasma tryptophan levels where only slightly lower in
patients. Carcinoid tumors consume large amounts of tryptophan
only intermittantly (de Vries et al. 2002). Consequently, plasma trypt-
ophan levels may be normal inbetween these periods. However, in
the psychiatric interview we did not collect information about the
temporal fluctuations of aggressive symptoms. It is therefore possi-
ble that patients suffering from aggressive impulse dysregulation
had plasma tryptophan levels in a normal range at the time of veni-
puncture. This made the relation between aggressive behavior and
plasma tryptophan levels somewhat circumstantial. A second series
of studies was performed in patients treated with recombinant inter-
feron-a to treat viral hepatitis. Such a medication regimen is suppo-
sed to affect the availability of tryptophan continuously (MacKenzie
et al. 1999). In these studies, the biochemical and psychiatric mea-
surements were performed before and during the tryptophan-deple-
ted state. In this study, psychopathology was assessed by a psychi-
atrist blind for the patients' biochemistry. We now observed signifi-
cant correlations between aggressive behavior and decreased plasma tryptophan concentration separating patients suffering from aggressive impulse dysregulation from those that did not. These results together strongly suggest that the observed behavioral changes were the consequence of altered tryptophan metabolism. In line with abundant literature on this issue, we suppose that the low tryptophan found in interferon treated and carcinoid patients compromises cerebral 5-HT neurotransmission (Bender 1983). For several decades, 5-HT has been associated with symptoms of depression, anxiety and impaired impulse control. To our surprise, no depressive symptoms were present in our patients. DSM IV classification of these patients led to the unspecific diagnosis "personality change due to a medical disorder". Compromised 5-HT neurotransmission has been linked to aggressive behavior in depressive patients (van Praag et al. 1987) and depressive disease marked by anger especially responds to SSRI treatment (Fava et al. 1998). Core depressive symptoms such as low self esteem, depressed mood and anhedonia were not present in our patients. Instead, we observed superior performance on some cognitive tasks by carcinoid patients.

Research on the relation between 5-HT and psychopathology traditionally focussed on depressive disease. One of the key findings relating 5-HT to depression was the assumption that 5-HT reuptake inhibitors have antidepressant effects (Kuhn 1965). Further clues originate from the symptoms developing in patients receiving the antihypertensive drug reserpine which has monoamine depleting properties. Based on these findings, the monoamine hypothesis of depression was postulated according to which a relative deficiency of cerebral monoamines, notably 5-HT, exists in depression (Coppen1969). In the following years, many studies were performed in which possible aberrations of the brain 5-HT system in depressive patients were studied. Decreased brain 5-HT turnover as measured by the content of 5-HIAA in CSF, obtained by lumbar punction, was observed in unmedicated depressed patients in several studies performed between '66 (Ashcroft 1966) and '84 (Asberg et al. 1984). However, these findings were outnumbered more then twofold by negative reports between '63 (Fotherby et al. 1963) and '97 (Geracioti et al. 1997).
Studies performed after administration of probenecid, that blocks the transport of 5-HIAA from CSF, yielded more positive results. Of seven CSF studies with probenecid comparing 5-HIAA levels between depressive patients and controls, five found decreased 5-HIAA in patients (Korf et al. 1971). Decreased CSF content of 5-HIAA has been reported consistently in patients suffering from hostile impulsive behavior such as aggressive suicide (Asberg 1976), violent offence and impulsive arsonism (Virkkunen et al. 1987). Many methodological issues are challenged in CSF studies. CSF 5-HIAA is related to age, sex body height, circadian and seasonal rhythms, diet, physical activity, puncture localisation amount of CSF drawn and analytical methods (Brown et al. 1990). In fact, lumbar CSF content of 5-HIAA may not even correlate with brain levels of 5-HIAA (Gjerris 1988). A more accessible manner to assess brain 5-HT production is to measure the plasma level of precursor amino acid tryptophan. Over 50 studies found decreased plasma tryptophan levels in depressive patients (Coppen 1988). Negative reports are substantially smaller in number (Sarrias 1987, Moller 1979). The decrease is correlated with vital symptoms, especially with weight loss (Anderson et al. 1990). Since tryptophan is the least abundant essential amino acid it is extremely sensitive to dietary depletion. Therefore, low plasma tryptophan levels are likely to be the result, rather than the cause of depression. Another manner to peripherally measure the status of the cerebral 5-HT system is to study the 5-HT transporter on blood platelets. Free 5-HT in the blood is taken up by platelets with a 5-HT transporter encoded by the same gene as the cerebral 5-HT pump that is blocked by many antidepressants. Therefore, in many studies performed in the eighties and nineties, the binding capacity of blood platelets for tritiated imipramine has been compared between depressive and healthy subjects. Most studies do report decreased binding capacity in unmedicated patients (for review see Ellis and Salmond '94). Some authors could not find decreased binding using the more specific ligand for the 5-HT transporter, paroxetine (Rosel 1997) but some could (Nemeroff 1994). The implications of these findings are not clear. It could be that due to decreased intake of tryptophan less 5-HT is available in the blood of depressive patients. Downregulation of the 5-HT transporter of
platelets under these circumstances might be an important homeostatic mechanism in the regulation of plasma free 5-HT levels (Thomas and Stocker 1999). Platelets possess the 5-HT2 receptor. In the nineties, about 11 studies appeared comparing the amount of these receptors between depressive patients and healthy subjects. Seven of these studies found 5-HT receptor upregulation in platelets of patients (Pandey 1995). Also in the last 2 decades of the previous century, numerous studies have been performed measuring the output of hormones which secretion is under control of the 5-HT system after administration of a 5-HT agonist. The hormones cortisol, prolactin and growth hormone were used as such. As 5-HT agonists served its natural precursors tryptophan and 5-hydroxytryptophan but also the 5-HT releasing agent fenfluramine and finally postsynaptically acting agonists of the 5-HT system such as ipsapirone and buspirone were used. Unfortunately, hormonal reactions to these compounds were highly inconsistent. Both blunted and enhanced cortisol responses are found after administration of 5-HTP to depressive patients compared to controls (Birmaher 1997, Meltzer 1984). Divergent hormonal reactions to tryptophan have been reported (Westenberg 1982, Deakin 1990). After fenfluramine administration blunted and normal responses are observed in depressed patients equally divided over the studies (Park 1996, Lucey 1992). Neuroendocrine challenge studies with postsynaptically acting agents also yielded inconsistent data (Price 1997, Meltzer 1994, Meltzer 1995). Blunted responses in neuroendocrine challenge studies are considered to be the result of postsynaptic 5-HT receptor hyposensitivity. This does not seem to be consistent with the hypothesis of pathological 5-HT deficiency as postulated in the monoamine hypothesis for depression since the postsynaptic 5-HT receptors do hypersensitize when the natural ligand decreases as shown by enhanced secretion of cortisol in response to i.v. infusion of tryptophan after dietary depletion of the precursor of 5-HT, tryptophan (Price et al. 1998). It has to be noted that in this experiment acute responses to tryptophan depletion were measured while in patients chronic conditions may apply. Altogether, results from neuroendocrine studies are difficult to interpret. Most authors propose a postsynaptic hyposensitivity in the 5-HT system of depressive patients. In
the nineties, dietary depletion of tryptophan has been extensively applied to study the possible involvement of 5-HT in depression. Most studies found a mild increase of depressive symptoms in unmedicated patients (Delgado et al. 1995). In fact, most psychiatric symptoms are provoked after tryptophan depletion according to the diagnosis of participants (Weltzin et al. 1995, Kent et al. 1996). In conclusion, the involvement of the 5-HT system in the etiology of depression has not convincingly been demonstrated despite of extensive research. Furthermore, all disturbances of the 5-HT system observed in depressive patients have proven to be highly unspecific for this, or any, diagnosis. Moreover, recent meta-analyses show that antidepressive effects of SSRIs are for over 80% mimicked by placebo so the role of 5-HT in the therapeutic effect can be questioned (Kirsch and Irving 2002). A recent review indicates that genetic studies have not convincingly revealed genes involved in 5-HT neurotransmission specific for depression (Arango et al. 2003). With regard to impulsive aggression and suicidal behavior the genetic link with 5-HT has been established by many authors. This link may be caused by the effects of 5-HTergic neurotransmission on irritable, impulsive and aggressive behavior (Zalsman et al. 2002). The pattern of 5-HT associated complaints as we observed does not fit in any syndrome defined by the DSM IV. Classification difficulties might explain why depression according to DSM IV criteria has been reported very inconsistently in somatic patient groups. For example, in patients treated with recombinant interferon-alpha depression rates varying from 3% to 45% have been reported (Okanoue et al. 1996, Musselman et al. 2001). Therefore, we conclude that 5-HT does not play a role in depression but that it serves a role in the accomplishment of behavior in unbenefficial somatic states.

Dietary and inflammation associated decrease of plasma tryptophan and the consequences have been studied in a large variety of species (chapter 9). These studies point out that the mechanism of tryptophan and consequently 5-HT depletion is evolutionary conserved and related with aggressive impulse regulation and social rank. These findings, at least those concerning aggressive impulse regu-
lation, are similar to our observations. In the studies we performed in carcinoid patients and patients treated with interferon-α, severe
ness of aggressive symptoms diverted strongly among patients exhi-
biting plasma tryptophan depletion for reasons we do not under-
stand.

In primates, a functional polymorphism in the promoter region of the
5-HT transporter gene exists. The short allele is related to decreased
production of the transporter. A recent study showed that early child-
hood abuse was related to psychiatric symptoms only in patients
with 1 or 2 copies of the short allele (Caspi 2003). This suggests that
gene environment interactions determine the output of the 5-HT
system and the vulnerability of an individual to develop symptoms
during compromising experiences. It is therefore possible that fluctu-
ation of plasma tryptophan level alone is not sufficient to cause
psychopathology and that interaction with genetic make up takes
place. These factors have to be taken into account in further studies
into the behavioral pattern of tryptophan depleted somatic patients.
When childhood experiences in part determine the function of the 5-
HTergic system, its response pattern might elucidate features that
are of psychiatric diagnostical value. Environmentally induced
heterogeneity of the 5-HT system may also explain the divergent hor-
monal responses observed in neuroendocrinological challenge stu-
dies mentioned earlier.

The work described in this thesis suggests that tryptophan depletion
has a physiological function. Tryptophan is degraded for over 99% un-
der physiological circumstances presumably to facilitate a switch
towards depletion when required. The coupling of plasma tryptop-
han levels and behavior is via brain 5-HT neurotransmission which
has a role in the adaptation to unbeneficial circumstances by modu-
ating brain function. Although no relation between dysfunction of the
5-HT system in the etiology of any specific psychiatric syndrome has
been established, symptoms of aggressive impulse dysregulation
are associated consistently to decreased 5-HT neurotransmission.

Until now, no data are available on individual features and sensitivi-
ty to tryptophan depletion. Monitoring of plasma tryptophan levels
may be helpful to identify patients suffering from increased aggression. However, this is difficult because no reference values are available and decrease rather than absolute plasma level may be indicative for the presence of aggressive impulse dysregulation. Therefore, history information is essential. However, in somatic patients, complaints of this order are not discussed. Questions such as "have you been in a quarrel more often lately?" could be asked to both the patient and his or her relatives. Plasma tryptophan levels may be directive in the choice of drugs. Serotonergically acting agents such as SSRI's might alleviate symptoms. However, these drugs need a certain serotonergic tone to work and with too low tryptophan levels the tone may be insufficient. Therefore, postsynaptically acting drugs such as mirtazapine (chapter 6) may be considered. We used this drug initially for its non SSRI characteristics because in carcinoid patients SSRI's are possibly not tolerated (Noyer et al. 1997). In addition, psychoeducation to both the patient and his or her relatives is important. Unlike many other aggressive patients, these persons themself suffer from behavior that usually is considered as not fitting to the former and healthy personality. It is therefore reassuring for patient and relatives to hear something about the background of these complaints. Also for (para) medics it will be useful to know more about behavioral disturbances in somatic patients. Knowledge on this subject is important because there seems to exist a behavioral counterpart of somatic disease. The psychopathology has a rather consistent pattern: irritability, increased alertness and aggressive impulsive dysregulation. Ultimately, this knowledge should be used for a further optimisation of handling of somatic patients.