J. Pharm. Pharmacol. 1999, 51: 723–728
Received November 27, 1998
Accepted January 13, 1999

Effects of *Hypericum perforatum* on Levels of 5-Hydroxytryptamine, Noradrenaline and Dopamine in the Cortex, Diencephalon and Brainstem of the Rat

G. CALAPAI, A. CRUPI*, F. FIRENZUOLI†, G. COSTANTINO, G. INFERRERA, G. M. CAMPO AND A. P. CAPUTI

*Institute of Pharmacology, School of Medicine, University of Messina, Piazza XX Settembre 4, I-98122 Messina, *Pharmalife-Italia, Airuno (LC) and †Service Phytotherapy, Hospital S. Giuseppe, ASL n. 11 Empoli, Italy*

Abstract

The plant *Hypericum perforatum* is used in folk medicine to treat several diseases and research attention has been recently focused on its antidepressant action. Hypericin and flavonoids are the most important constituents of the plant, but the exact role of these compounds in the effects of hypericum on mood disorders is not well known. We have investigated the contribution of these compounds to the antidepressant effects of hypericum.

The effects of acute administration of hypericum extracts on levels of 5-hydroxytryptamine (5-HT), tryptophan, 5-hydroxyindoleacetic acid (5-HIAA), noradrenaline and dopamine in the cortex, diencephalon and brainstem was evaluated. The levels of these neurotransmitters were measured 1 h and 24 h after administration of two different extracts, one containing 0·3% hypericin and 6% flavonoids (Li 160; 25–500 mg kg^{-1}), the other containing 0·3% hypericin and 50% flavonoids (Ph-50; 25–500 mg kg^{-1}). Results from experiments performed on 5-HT turnover were compared with the effects of fluoxetine (10–80 mg kg^{-1}). Li 160, Ph-50 and fluoxetine induced a significant increase in the 5-HT content of the cortex. In the diencephalon Ph-50, but not Li 160 or fluoxetine, elicited an increase in 5-HT and 5-HIAA levels. In the brainstem Ph-50 and fluoxetine caused an increase in 5-HT content; Li 160 did not change neurotransmitter content. Both Li 160 and Ph-50 caused increases of noradrenaline and dopamine in the diencephalon. In the brainstem only Ph-50 induced an increase in noradrenaline content.

Our data confirm that acute administration of hypericum extracts modifies the levels of neurotransmitters involved in the pathophysiology of mood disorders. When the extracts contain a higher concentration of flavonoids the effects are more widespread and involve brain regions such as diencephalon and brainstem that are implicated in depression.

In recent years *Hypericum perforatum* has been investigated for its therapeutic effects on mood disorders, and its antidepressive action has been demonstrated in animals and in man (De Smet & Nolen 1996; Linde et al 1997; Özturk 1997). *Hypericum perforatum* contains several compounds of biological interest. The most important constituents are the naphthodianthrone hypericin (Brockmoller et al 1997) and a broad spectrum of flavonoids (Kartnig et al 1996). More recently, hyperforin, another constituent of *Hypericum perforatum*, has been indicated as the possible major active principle responsible for the observed clinical efficacy (Chatterjee et al 1998). The role and the mechanism of action of these different compounds is unclear. The most cited mechanisms of action are inhibition of the degradative enzymes monoaminooxidases (Suzuki et al 1984) and catechol-*o*-methyltransferase (Thiede & Walper 1994). Other authors have reported the inhibitory activity of hypericum extract on synaptosomal uptake of 5-hydroxytryptamine and noradrenaline (Perovic & Müller 1995).

On the basis of these results, and with the aim of evaluating the role of flavonoids in the anti-

Correspondence: G. Calapai, Institute of Pharmacology, School of Medicine, University of Messina, Piazza XX Settembre 4, I-98122 Messina, Italy.

depressant action of hypericum, we have studied the effects of two hypericum extracts, containing the same amount of hypericin but different concentrations of flavonoids, on levels of tryptophan, 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), noradrenaline and dopamine in discrete brain regions such as the cortex, diencephalon and brainstem of the rat. We compared the results from experiments performed on 5-HT turnover with those obtained with fluoxetine (10–80 mg kg^{-1}), a selective 5-hydroxytryptamine reuptake inhibitor with antidepressant activity (Mourilhe & Stokes 1998).

Materials and Methods

Animals

Experiments were conducted on adult male Sprague–Dawley rats, 280–320 g. The animals were housed at a constant temperature of 22 ± 2°C under a 12-h light–dark cycle (lights on at 0600 h), with free access to Purina rat chow pellets and tap water, unless otherwise stated. Acclimatization and experimentation were conducted in accordance with internationally accepted principles and national laws concerning the care and use of laboratory animals.

Brain content of tryptophan, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid

To measure the brain levels of tryptophan, 5-HT, 5-HIAA, noradrenaline and dopamine the animals were killed by decapitation under ether anaesthesia 1 h after treatment and the brain was rapidly removed and placed on a cold plate. Cortex, diencephalon and brainstem were quickly dissected out and frozen at −80°C. For evaluation of tryptophan, 5-HT and 5-HIAA, brain samples were homogenized in perchloric acid (0·2 M; 1 mL). Cell debris was removed by centrifugation at 6000 *g* for 10 min, the pellet was discarded, and the supernatant was filtered. The samples obtained were frozen at −80°C and stored until the assay. Sample tryptophan, 5-HT and 5-HIAA content were determined by high-performance liquid chromatography (HPLC) with electrochemical detection (Squadrito et al 1994). Tryptophan was expressed as μmol (g fresh tissue)$^{-1}$; 5-HT and 5-HIAA were expressed as nmol (g fresh tissue)$^{-1}$.

Brain content of noradrenaline and dopamine

For tissue catecholamine analysis cerebral specimens were stored at −80° until assay. Assay was performed by the HPLC method of De Saint Blanquat et al (1987) with some modifications. Briefly, tissue homogenate (1 mL) in polycarbonate tubes was treated with the internal standard dihydroxybenzylamine hydrobromide and activated alumina (10 mg). After vortex-mixing for 10 min, the supernatant was discarded and the alumina washed three times with Tris-HCl buffer (pH 8·6, 0·1 M). Catecholamines were then separated from the alumina by addition of $HClO_4$ (0·1 M; 200 μL). After centrifugation at 10 000 *g* for 5 min at 4°C, the supernatant was recovered and filtered and HPLC analysis was performed on a 50-μL sample.

HPLC was performed with a Kontron (Everett, USA) model 422 Master, solvent-delivery module linked with a Coulochem Model 5100A coulometric electrochemical detector (ESA, Bedford, MA) which monitored the analytical cell (model 5011; ESA) and the conditioning cell (model 5021; ESA). The detector was connected to a Shimadzu (Kyoto, Japan) model CR-3A automatic integrator. The column used was an 80 mm × 4·6 mm i.d., 3 μm particle size, HR-80 (ESA). The mobile phase was a solution of monobasic sodium phosphate (6·9 g), heptanesulphonic acid (250 mg) and EDTA (80 mg) in pure water (900 mL); the pH of the solution was adjusted to 3 by addition of phosphoric acid. Before filtering under vacuum methanol (100 mL) was added. The flow rate was 1 mL min^{-1} at room temperature. Detector potentials were: conditioning cell +0·3 V; detector 1 0·00 V; detector 2 −0·25 V. Calibration chromatograms of accurately extracted standards of noradrenaline and dopamine were also run every time for peak identification and quantitation. Noradrenaline and dopamine were expressed as nmol (g fresh tissue)$^{-1}$.

Test substances

A commercially available hypericum extract (Li 160; Jarsin Lichtwer Pharma GmbH) containing 0·3% hypericin and 6% flavonoids and a preparation of hypericum standardized to flavonoids and containing 0·3% hypericin and 50% flavonoids (Ph-50 Pharmalife-Italia) were used. Test substances were dissolved in saline and administered orally by gastro–oesophageal gavage, as two administrations 24 h and 1 h before the experiments, between 1000 and 1200 h. Animals treated only with saline served as control group.

Statistical analysis

All statistical procedures were performed by use of the SPSS statistical software package, V.6.1.3

(SPSS, Chicago, IL). Data analysis was performed by analysis of variance (one-way test) with the Scheffé post-hoc test for multiple comparisons. Data are expressed as the means ± s.e.m. Statistical significance was set at $P < 0{\cdot}05$.

Results

Effects on brain content of tryptophan, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid

Both extracts of hypericum induced a significant increase in the 5-HT content of the cortex. This effect was evident for doses of Li 160 or Ph-50 $\geq 125\,mg\,kg^{-1}$. Treatment of the same brain region with fluoxetine caused a significant and dose-dependent increase of both 5-HT and 5-HIAA. Analysis of the 5-HT, tryptophan and 5-HIAA content of the diencephalon gave different results. In this region neither Li 160 nor fluoxetine administration changed the tryptophan, 5-HT and 5-HIAA content. Administration of $\geq 125\,mg\,kg^{-1}$ Ph-50 extract dose-dependently increased the 5-HT and 5-HIAA content in comparison with the control group. In the brainstem Ph-50 and fluoxetine had similar effects, significantly increasing 5-HT content, at doses of 250 and $500\,mg\,kg^{-1}$, and of 20 and $40\,mg\,kg^{-1}$, respectively. Treatment with Li 160 did not change 5-hydroxytryptamine turnover in the brainstem. The was no statistical differences among the groups between tryptophan and 5-HIAA levels observed in this region (Table 1).

Effects on the brain content of noradrenaline and dopamine

Acute administration of Li 160 or Ph-50 did not affect the levels of noradrenaline or dopamine in the cortex. Examination of brain samples obtained from the diencephalon revealed that acute administration of Li 160 or Ph-50 elicited significant and dose-dependent increases of both noradrenaline and dopamine in this region. This effect was evident with doses of 250 and $500\,mg\,kg^{-1}$. In the brainstem only Ph-50 elicited a significant and dose-dependent increase in noradrenaline content (Table 2).

Discussion

Hypericin (the constituent on which most commercially available preparations of hypericum extracts are standardized) is regarded as the active principle in extracts of *Hypericum perforatum* (Müldner & Zöller 1984). Some reports have shown that hypericin inhibits monoaminooxidases (Suzuki et al 1984), but other authors have failed to confirm this effect (Demisch et al 1989; Thiede & Walper 1994). Recent studies did not confirm the key antidepressant role of hypericin, raising the question of which other constituents of the hypericum extracts might be involved. In particular, some findings suggest the presence of flavonoids might be responsible for monoaminooxidase inhibition (Bladt & Wagner 1994).

Several lines of evidence indicate that enhancement of 5-HT neurotransmission might underlie the therapeutic response to different types of antidepressant treatment (Blier & de Montigny 1994). In the current work, measurement of 5-HT turnover after acute administration of hypericum extracts containing different concentrations of flavonoids revealed changes in 5-HT content, although in different ways. Administration of extracts of hypericum induced an increase in the 5-HT content of the cortex. A similar effect has been observed after acute administration of selective 5-hydroxytryptamine reuptake inhibitors, which induce a small and transient increase in extracellular 5-HT concentrations in the rat frontal cortex (Bel & Artigas 1993). Our data showed that orally acute administration of high doses of fluoxetine reproduces this effect in the cortex. At the diencephalic level, a significant and dose-dependent 5-HT content increase, and enhancement of 5-HIAA levels in the same region, were observed only after administration of the extract containing more flavonoids. Tryptophan content was not affected by treatment with either of the extracts, indicating that the effect might be because of action on the release or reuptake of 5-HT.

Dysfunction of the brain noradrenergic system is thought be involved in mood disorders (Montgomery 1997). Measurement of noradrenaline after acute administration of hypericum extracts showed that both kinds of extract increased neurotransmitter levels in the diencephalon. Extract Ph-50, containing more flavonoids, also increased the noradrenaline content of the brainstem. In the light of recent findings suggesting a role of the brainstem in the control of mood (Becker et al 1997), these changes indicate that this region of the brain might be a target for the action of hypericum. The effect of antidepressants requires several weeks of treatment and any extrapolation from data collected after acute administration needs caution.

The differences observed in the effects on the 5-HT content of the brain regions studied leads to the conclusion that the two extracts of hypericum used in this study act differently. On the cortex, both

Table 1. Effects of acute oral administration of extracts of *Hypericum perforatum* and of fluoxetine on the levels of tryptophan, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in the cortex, diencephalon and brainstem of the rat.

Treatment ($mg\,kg^{-1}$)	Tryptophan ($\mu mol\,g^{-1}$)	5-Hydroxytryptamine ($nmol\,g^{-1}$)	5-Hydroxyindoleacetic acid ($nmol\,g^{-1}$)
Cortex			
Saline	0·34 ± 0·03	0·23 ± 0·02	0·27 ± 0·03
Ph-50 (62·5)	0·32 ± 0·04	0·25 ± 0·08	0·30 ± 0·06
Ph-50 (125)	0·37 ± 0·07	0·66 ± 0·15*	0·82 ± 0·17*
Ph-50 (250)	0·35 ± 0·06	1·65 ± 0·61*	1·81 ± 0·53*
Ph-50 (500)	0·36 ± 0·04	1·91 ± 0·67*	2·72 ± 0·65*¤
Li 160 (62·5)	0·35 ± 0·04	0·26 ± 0·04	0·34 ± 0·03
Li 160 (125)	0·44 ± 0·06	0·68 ± 0·17*	0·84 ± 0·21*
Li 160 (250)	0·39 ± 0·03	1·52 ± 0·54*	1·38 ± 0·47*
Li 160 (500)	0·47 ± 0·07	2·05 ± 0·69*	2·11 ± 0·05*
Fluoxetine (10)	0·35 ± 0·04	0·27 ± 0·03	0·33 ± 0·04
Fluoxetine (20)	0·39 ± 0·03	0·71 ± 0·16*	1·04 ± 0·21**
Fluoxetine (40)	0·41 ± 0·05	1·85 ± 0·41**	2·27 ± 0·45**
Fluoxetine (80)	0·65 ± 0·05**	3·17 ± 0·71**‡	3·91 ± 0·45**‡‡
Diencephalon			
Saline	0·25 ± 0·06	1·56 ± 0·23	3·07 ± 0·40
Ph-50 (62·5)	0·29 ± 0·07	1·62 ± 0·31	3·25 ± 0·51
Ph-50 (125)	0·31 ± 0·04	3·27 ± 0·69*	4·33 ± 0·58
Ph-50 (250)	0·24 ± 0·03	4·93 ± 0·58***	5·13 ± 0·50**
Ph-50 (500)	0·26 ± 0·04	6·00 ± 0·69***†	5·68 ± 0·54**
Li 160 (62·5)	0·31 ± 0·04	1·74 ± 0·32	2·77 ± 0·45
Li 160 (125)	0·29 ± 0·05	1·63 ± 0·34	2·44 ± 0·41
Li 160 (250)	0·35 ± 0·06	1·55 ± 0·27	3·03 ± 0·53
Li 160 (500)	0·27 ± 0·05	1·87 ± 0·31	2·51 ± 0·50
Fluoxetine (10)	0·31 ± 0·05	1·59 ± 0·21	2·91 ± 0·38
Fluoxetine (20)	0·29 ± 0·04	1·94 ± 0·41	3·14 ± 0·33
Fluoxetine (40)	0·31 ± 0·03	1·81 ± 0·45	2·85 ± 0·37
Fluoxetine (80)	0·30 ± 0·04	2·67 ± 0·59	2·90 ± 0·42
Brainstem			
Saline	0·05 ± 0·01	6·82 ± 0·59	4·81 ± 0·53
Ph-50 (62·5)	0·07 ± 0·02	6·45 ± 0·56	5·67 ± 0·79
Ph-50 (125)	0·04 ± 0·01	7·89 ± 0·51	6·21 ± 0·94
Ph-50 (250)	0·03 ± 0·01	8·61 ± 0·47*	6·89 ± 1·07
Ph-50 (500)	0·03 ± 0·01	9·49 ± 0·70*	5·41 ± 1·15
Li 160 (62·5)	0·06 ± 0·01	7·15 ± 0·66	5·13 ± 0·68
Li 160 (125)	0·05 ± 0·01	7·32 ± 0·57	5·67 ± 0·73
Li 160 (250)	0·03 ± 0·01	7·44 ± 0·61	5·07 ± 0·61
Li 160 (500)	0·03 ± 0·01	7·04 ± 0·74	3·39 ± 0·73
Fluoxetine (10)	0·04 ± 0·01	7·08 ± 0·52	5·24 ± 0·51
Fluoxetine (20)	0·07 ± 0·02	7·92 ± 0·61	5·39 ± 0·65
Fluoxetine (40)	0·05 ± 0·01	8·71 ± 0·59*	5·81 ± 0·74
Fluoxetine (80)	0·05 ± 0·01	9·67 ± 0·85*	5·47 ± 0·68

Data analysis was performed by analysis of variance one-way test with Scheffé post-hoc test for multiple comparisons. Each group comprised six animals. Data are expressed as means ± s.e.m. *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$ compared with saline; †$P < 0·05$ compared with Ph-50 ($125\,mg\,kg^{-1}$); ‡$P < 0·05$, ‡‡$P < 0·01$ compared with fluoxetine ($20\,mg\,kg^{-1}$).

hypericum extracts have similar effects, whereas changes in the 5-HT and noradrenaline content of the brainstem and diencephalon suggest other considerations. Increased activity of the hypothalamic–pituitary–adrenal axis in depression has been reported (Maes et al 1991) and it has also been proposed that abnormality of monoamine function plays a role in the pathogenesis of this disorder (Mokrani et al 1997). This disturbance is related to central corticotropin-releasing hormone hypersecretion (Holsboer et al 1992) and subsensitivity in negative feedback by glucocorticoids (Gomez et al 1998). It has also been shown that depletion of 5-HT in the hippocampus can reduce the negative feedback effects of glucocorticoids on the hypothalamic–pituitary–adrenal axis (Seckl & Fink 1991) thus inducing excessive corticosteroid secretion. Enhancement of 5-HT in the diencephalon observed in our work seems to reflect a different mode of action of hypericum extracts that could be related to the presence of more flavonoids, whereas the extract standardized on hypericin did not have the same effect in this region.

Elevation of dopamine transmission might be a final common pathway responsible for at least part of the spectrum of behavioural actions of anti-

Table 2. Effects of acute oral administration of extracts of*Hypericum perforatum* on the noradrenaline and dopamine content of the cortex, diencephalon and brainstem of the rat.

Treatment ($mg\,kg^{-1}$)	Noradrenaline ($nmol\,g^{-1}$)	Dopamine ($nmol\,g^{-1}$)
Cortex		
Saline	10·73 ± 2·1	116·60 ± 6·0
Li 160 (62·5)	10·20 ± 1·7	108·12 ± 4·4
Li 160 (125)	10·39 ± 1·6	110·63 ± 5·7
Li 160 (250)	11·12 ± 1·8	109·41 ± 6·1
Li 160 (500)	11·45 ± 1·8	110·62 ± 6·6
Ph-50 (62·5)	10·64 ± 1·4	110·41 ± 5·3
Ph-50 (125)	10·91 ± 1·6	111·73 ± 5·8
Ph-50 (250)	11·51 ± 1·3	110·56 ± 5·4
Ph-50 (500)	11·93 ± 1·4	112·35 ± 5·4
Diencephalon		
Saline	23·82 ± 1·1	11·20 ± 0·69
Li 160 (62·5)	22·83 ± 1·3	11·31 ± 0·71
Li 160 (125)	23·64 ± 1·0	11·72 ± 0·54
Li 160 (250)	27·91 ± 1·1*	13·32 ± 0·81
Li 160 (500)	31·15 ± 0·9***†	18·88 ± 0·80***
Ph-50 (62·5)	22·43 ± 1·5	11·00 ± 0·62
Ph-50 (125)	24·85 ± 1·2	13·09 ± 0·70
Ph-50 (250)	28·92 ± 1·3**	14·73 ± 0·84*
Ph-50 (500)	31·65 ± 0·8***	20·36 ± 0·81***‡
Brainstem		
Saline	18·78 ± 1·1	2·96 ± 0·16
Li 160 (62·5)	18·45 ± 0·7	2·91 ± 0·14
Li 160 (125)	18·20 ± 0·8	2·85 ± 0·17
Li 160 (250)	18·77 ± 0·6	2·95 ± 0·20
Li 160 (500)	19·02 ± 0·6	2·87 ± 0·12
Ph-50 (62·5)	18·31 ± 0·6	2·88 ± 0·18
Ph-50 (125)	18·94 ± 0·6	2·91 ± 0·12
Ph-50 (250)	20·91 ± 0·5*	2·90 ± 0·15
Ph-50 (500)	22·62 ± 0·7**	2·88 ± 0·10

Data analysis was performed by analysis of variance one-way test with Scheffé post-hoc test for multiple comparisons. Each group comprised six animals. Data are expressed as means ± s.e.m. $*P < 0{\cdot}05$, $**P < 0{\cdot}01$, $***P < 0{\cdot}001$ compared with saline; $\dagger P < 0{\cdot}05$ compared with Li 160 ($250\,mg\,kg^{-1}$); $\ddagger P < 0{\cdot}001$ compared with Ph-50 ($250\,mg\,kg^{-1}$).

depressant drugs. Chronic administration of antidepressants provokes a sensitization and enhanced expression of dopaminergic receptors (Bowden et al 1997b), and evidence of significantly reduced dopamine turnover in depressed suicides has been observed (Bowden et al 1997a). It has been observed that hypericum treatment increases dopamine levels within the central nervous system (Müldner & Zöller 1984). Moreover, dopaminergic antagonists such as haloperidol or sulpiride reduce the antidepressant activity of hypericum in rodents (Butterweck et al 1997). Our data confirm this hypothesis, suggesting involvement of the dopaminergic system in the effects of hypericum on mood disorders.

The observation that hypericum extracts modulate the tone of several neurotransmitters in the brain in a specific manner depending on the concentrations of the active compounds contained, is in agreement with previous findings showing that inhibition of monoaminooxidases is more evident with hypericum extract fractions containing higher concentration of flavonoids (Bladt & Wagner 1994), thus supporting the importance of the role of flavonoids. Another active principle, hyperforin, has recently been implicated as being responsible for the antidepressant action of an extract of *Hypericum perforatum*. It has been observed that the presence of a higher concentration of hyperforin in hypericum extracts increases clinical efficacy (Lookmann et al 1998). Hyperforin has been found to be rather unstable when exposed to heat and light (Nahrstedt & Butterweck 1997), which reduces its role in the antidepressive effects induced by administration of hypericum extracts.

Acute administration of the extract containing a higher concentration in flavonoids (Ph-50) leads to an increase in 5-HT levels in the diencephalon and brainstem also. This last observation might be important because the pharmacological manipulation of the hypothalamic–pituitary–adrenal axis seems to have considerable promise for the development of novel approaches to depression (Barden 1996).

In conclusion, our data show that in the rat, acute administration of large doses of extracts of hypericum can change the content of neurotransmitters, e.g. 5-HT, noradrenaline and dopamine, involved in the pathophysiology of mood disorders. However, when the extracts administered contain a higher concentration of flavonoids the effects are evident more widely throughout the brain, involving brain regions such as diencephalon and brainstem which have recently been implicated in the pathophysiology of depression. Because high doses have been used in this study, the clinical relevance of the data is not automatic; they could, however, contribute to elucidating the mechanism of action of *Hypericum perforatum* extracts.

References

Barden, N. (1996) Modulation of glucocorticoid receptor gene expression by antidepressant drugs. Pharmacopsychiatry 29: 12–22

Becker, T., Becker, G., Seufert, J., Hofmann, E., Lange, K. W., Naumann, M., Lindner, A., Reichmann, H., Riederer, P., Beckmann, H., Reiners, K. (1997) Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. J. Neurol. Neurosurg. Psychiatry 63: 590–596

Bel, N., Artigas, F. (1993) Chronic treatment with fluvoxamine increases extracellular 5-hydroxytryptamine in frontal cortex but not in raphe nuclei. Synapse 15: 243–245

Bladt, S., Wagner, H. (1994) Inhibition of MAO by fractions and constituents of Hypericum extract. J. Geriatric. Psychiatr. Neurol. 7: S57–S59

Blier, P., de Montigny, C. (1994) Current advances and trends in the treatment of depression. Trends Pharmacol. Sci. 15: 220–226

Bowden, C., Cheetam, S. C., Lowther, S., Katona, C. L., Crompton, M. R., Horton, R. W. (1997a) Reduced dopamine turnover in the basal ganglia of depressed suicides. Brain Res. 769: 135–140

Bowden, C., Theodorou, A. E., Cheetam, S. C., Lowther, S., Katona, C. L., Crompton, M. R., Horton, R. W. (1997b) DA D1 and D2 receptor binding sites in brain samples from depressed suicides and controls. Brain Res. 752: 227–233

Brockmoller, J., Reum, T., Bauer, S., Kerb, R., Hubner, W. D., Roots, I. (1997) Hypericin and pseudohypericin: pharmacokinetics and effects on photosensitivity in humans. Pharmacopsychiatry 30 (Suppl. 2) 94–101

Butterweck, V., Wall, A., Liefländer-Wulf, U., Wintherhoff, A., Nahrstedt, A. (1997) Effects of the total extract and fractions of *Hypericum perforatum* in animal assays for antidepressant activity. Pharmacopsychiatry 30: S117–S124

Chatterjee, S. S., Bhattacharrya, S. K., Wonnemann, M., Singer, A., Müller, W. E. (1998) Hyperforin as a possible antidepressant component of Hypericum extracts. Life Sci. 63: 499–510

Demisch, L., Hölzl, J., Gollnick, B., Kacmarczyk, P. (1989) Identification of MAO-type-A inhibitors in *Hypericum perforatum* L. (Hyperforat). Pharmacopsychiatry 22: 194

De Saint Blanquat, G., Lambouef, Y., Fritsch, P. (1987) Determination of catecholamines in biological tissues by liquid chromatography with coulometric detection. J. Chromatogr. 415: 388–392

De Smet, P. A., Nolen, W. A. (1996) St. John's wort as an antidepressant. Br. Med. J. 313: 241–247

Gomez, F., De Kloet, E. R., Armario, A. (1998) Glucocorticoid negative feedback on the HPA axis in five inbred rat strains. Am. J. Physiol. 274: R420–R427

Holsboer, F., Spengler, D., Heuser, I. (1992) The role of corticotropin-releasing hormone in the pathogenesis of Cushing's disease, anorexia nervosa, alcoholism, affective disorders and dementia. Progr. Brain Res. 93: 385–417

Kartnig, T., Gobel, I., Heydel, B. (1996) Production of hypericin, pseudohypericin and flavonoids in cell cultures of various Hypericum species and their chemotypes. Planta Med. 62: 51–53

Linde, K., Ramirez, G., Mulrow, C. D., Pauls, A., Weidenhammer, W., Melchart, D. (1997) St. John's wort for depression—an overview and meta-analysis of randomised clinical trials. Br. Med. J. 313: 253–258

Lookmann, G., Schüle, C., Baghal, T., Kleser, M. (1998) St. John's Wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. Pharmacopsychiatry 31: S54–S59

Maes, M., Vandervost, C., Suy, E., Minner, B., Raus, J. (1991) A multivariate study on the simultaneous urinary free cortisol, plasma cortisol, adrenocorticotropic hormone and β-endorphin escape from suppression by dexamethasone in melancholic patients. Acta Psychiatr. Scand. 83: 480–491

Mokrani, M. C., Duval, F., Crocq, M. A., Bailey, P., Macher, J. P. (1997) HPA axis dysfunction in depression: correlation with monoamine system abnormalities. Psychoneuroendocrinology 22 (Suppl. 1): S63–S68

Montgomery, S. A. (1997) Is there a role for a pure noradrenergic drug in the treatment of depression? Eur. Neuropsychopharmacol. 7 (Suppl. 1): S3–S9

Mourilhe, P., Stokes, P. E. (1998) Risks and benefits of selective 5-hydroxytryptamine reuptake inhibitors in the treatment of depression. Drug Safety 18: 57–82

Müldner, H., Zöller, M. (1984) Antidepressive Wirkung eines auf den Wirkstoffkomplex Hypericin standardisierten Hypericum-Extraktes. Arzneim. Forsch. 34: 918–920

Nahrstedt, A., Butterweck, V. (1997) Biologically active and other chemical constituents of the herb of *Hypericum perforatum*. Pharmacopsychiatry 30: S129–S134

Özturk, Y. (1997) Testing the antidepressant effects of Hypericum species on animal models. Pharmacopsychiatry 30: 125–128

Perovic, S., Müller, W. E. G. (1995) Pharmacological profile of Hypericum extract: effect on 5-hydroxytryptamine uptake by receptors. Arzneim. Forsch. 45: 1145–1148

Seckl, J. R., Fink, G. (1991) Use of in situ hybridization to investigate the regulation of hippocampal corticosteroid receptors by monoamines. J. Steroid Biochem. Mol. Biol. 40: 685–688

Squadrito, F., Calapai, G., Altavilla, D., Cucinotta, D., Zingarelli, B., Arcoraci, V., Campo, G. M., Caputi, A. P. (1994) Central 5-hydroxytryptaminergic system involvement in the anorexia induced by N^G-nitro-L-arginine, an inhibitor of nitric oxide synthase. Eur. J. Pharmacol. 255: 51–55

Suzuki, O., Katsumata, Y., Oya, M., Bladt, S., Wagner, H. (1984) Inhibition of monoamine oxidase by hypericin. Planta Med. 50: 272–274

Thiede, H. M., Walper, A. (1994) Inhibition of MAO and COMT by Hypericum extract and hypericin. J. Geriatric. Psychiatr. Neurol. 7: S60–S62