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The antidepressant mechanism of *Hypericum perforatum*

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Abstract

Clinical data indicate that hydroalcoholic extracts of *Hypericum perforatum* might be as valuable as conventional antidepressants in mild-to-moderate depression, with fewer side effects. One clinical trial using two extracts with different hyperforin contents indicated it as the main active principle responsible for the antidepressant activity. Behavioural models in rodents confirm the antidepressant-like effect of *Hypericum* extracts and also of pure hyperforin and hypericin. A hydroalcoholic extract lacking hyperforin also lacks the antidepressant-like effect. According to pharmacokinetic data and binding studies, it appears that the antidepressant effect of *Hypericum* extract is unlikely be due to an interaction of hypericin with central neurotransmitter receptors. The main in vitro effects of hyperforin (at concentrations of 0.1–1 μM) are non-specific presynaptic effects, resulting in the non-selective inhibition of the uptake of many neurotransmitters, and the interaction with dopamine D1 and opioid receptors. However, it is still not clear whether these mechanisms can be activated in vivo, since after administration of *Hypericum* extract brain concentrations of hyperforin are well below those active in vitro. In the rat, *Hypericum* extract might indirectly activate sigma receptors in vivo (through the formation of an unknown metabolite or production of an endogenous ligand), suggesting a new target for its antidepressant effects.

Keywords: *Hypericum perforatum*; Antidepressant; 5-HT uptake; Sigma receptor; Hypericin; Hyperforin

Introduction

Hypericum perforatum L., popularly called St. John's wort (SJW), is a herbaceous perennial plant long known for its putative medicinal properties including wound-healing, diuretic, antibiotic and antiviral effects (Bombardelli and Morazzoni, 1995). Although clinical trials have given contradictory

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results, nowadays, alcoholic extracts of SJW are mainly used for the treatment of mild-to-moderate forms of depression as an alternative to classic antidepressants, with a favourable side-effect profile (Linde and Mulrow, 2003). SJW extracts also consistently showed antidepressant-like properties in behavioural models in rodents (Butterweck et al., 1997; Ozturk, 1997; Chatterjee et al., 1998a,b; Gambarana et al., 1999; Gobbi et al., 1999; Panocka et al., 2000; Gobbi and Mennini, 2001). The active principle(s) responsible for the antidepressant effect, and the mechanism of action, are still under investigation. Here we summarize the main findings related to monoaminergic transmission, to highlight similarities (few) and differences (many) with known antidepressants, and compare the data obtained in vitro with the brain levels of the main constituents.

Constituents of *Hypericum perforatum* extract

The most common SJW preparations used as antidepressants are hydroalcoholic extracts of the aerial portion of the plant. These contain several natural products (Bombardelli and Morazzoni, 1995; Nahrstedt and Butterweck, 1997): flavonoids, proanthocyanidins, naphthodianthrones (including hypericin and pseudohypericin), and acylphloroglucinols (including hyperforin and adhyperforin). The concentrations and the proportions of the different constituents in the plant are closely related to the harvesting period, drying process and storage. Flavonoids account for about 2–4% of the hydroalcoholic extracts but their wide distribution in many plants suggests they are probably not related to the antidepressant properties of the extract.

Most interest initially focused on hypericin, which has been isolated in only a few other plants, also because it was initially described as a monoamine oxidase (MAO) inhibitor (Suzuki et al., 1984). Although later studies indicated that this effect was not clinically significant (see below), hypericin is nevertheless commonly used to standardize SJW extracts. Total hypericins usually amount to about 0.3% of hydroalcoholic extracts.

Attention has recently increasingly been paid to hyperforin, neglected at the beginning because of its instability in light and air (Erdelmeier, 1998). However, 1-5% hyperforin can be found and kept in the SJW extracts, if appropriately stored, for long periods (Chatterjee et al., 1998a,b). The importance of the drying and storage conditions is confirmed by the widely varying hyperforin content in commercial preparations of SJW extracts (Erdelmeier, 1998). This is an extremely important point when comparing preclinical or clinical studies using different experimental conditions, since the presence and the actual concentration of hyperforin in the preparation under study could be responsible for differences in the results (Guilhermano et al., 2003).

Which component of the *Hypericum perforatum* extract is responsible for the antidepressant effect?

Hypericin, the component used to standardize extracts, showed antidepressant-like properties in the forced swimming test in rats (Butterweck et al., 1998). Binding studies indicated it had nanomolar affinity only for dopamine D3 receptors (Butterweck et al., 2002) but micromolar affinities for other receptors (Raffa, 1998; Gobbi et al., 2001; Simmen et al., 2001; Butterweck et al., 2002). Plasma concentrations of hypericin in humans given pharmacologically effective doses of SJW extracts are in the nanomolar range

(Staffeldt et al., 1994; Brockmoller et al., 1997). The brain hypericin concentration reaches 8–40% of the plasma concentration, determined in mice using radiolabelled hypericin (Stock and Holzl, 1991). It thus appears that the antidepressant effects of SJW extracts are unlikely be due to hypericin interacting with central neurotransmitter receptors, with the exception of a possible interaction with rat dopamine D3 receptors. However, there is no evidence of the in vivo relevance of this effect.

The involvement of hyperforin in the antidepressant effect of the extracts is more consistently documented. One clinical trial showed the loss of antidepressant properties using an extract with 0.5% hyperforin content instead of 5% (Laakmann et al., 1998). Pure hyperforin has antidepressant properties in animal models of depression, and the potencies of different extracts closely correlate with their hyperforin content (Chatterjee et al., 1998a,b; Gambarana et al., 2001; Cervo et al., 2002). However, the brain concentrations of hyperforin in rats given pharmacologically active doses of SJW extract or hyperforin are less than 5 pmol/g (roughly less than 5 nM) (Cervo et al., 2002). Evaluation of hyperforin levels by high-performance liquid chromatography/tandem mass spectrometry in the brain of rats given three i.p. doses of hyperforin trimethoxybenzoate indicated brain concentration ranging 24 nM (Mennini et al., 2002). Similar results were obtained in mice after oral administration of pharmacologically active doses of hyperforin sodium salt or SJW exctract (Keller et al., 2003). These brain levels are possibly entirely related to compound's contribution from residual blood, and in any case, they are too low to support an interaction with the central mechanisms so far tested.

What is the mechanism of action?

It was initially suggested that the antidepressant effect of SJW extracts was due to the MAO-inhibitory properties of hypericin (Suzuki et al., 1984). However, this effect was obtained in vitro with concentrations of extracts too high (>100 μg/mL) to be achieved in vivo (Bladt and Wagner, 1994; Thiede and Walper, 1994), and no effect on MAO activity was detected ex vivo in rats given 100 mg/kg i.p. of the whole extract (Bladt and Wagner, 1994).

It was later reported that SJW extracts in vitro inhibited the synaptosomal uptake of 5-HT, DA and NA with high potency (Muller et al., 1997) and that most of this effect was due to hyperforin (Chatterjee et al., 1998a,b; Muller et al., 1998; Gobbi et al., 1999). However, the mechanism is different from that of the classic antidepressant "reuptake inhibitors", since the latter - but not hyperforin - interact with (and block) the monoamine transporter proteins (Gobbi et al., 1999; Singer et al., 1999; Gobbi et al., 2001; Butterweck et al., 2002; Roz et al., 2002).

The apparent inhibition of monoamine reuptake by hyperforin involves changes in intracellular H^+ and Na^+ concentrations (Singer et al., 1999) and/or of neurotransmitter storage in synaptic vesicles (Gobbi et al., 1999; Roz et al., 2002; Roz and Rehavi, 2003). These non-specific effects on presynaptic terminals may well explain the non-selective inhibition of the uptake of many neurotransmitters, including choline (Buchholzer et al., 2002) GABA and glutamate (Chatterjee et al., 1998a,b), and also the induction of monoamine, amino acids and acetylcholine release from synaptosomes (Gobbi et al., 1999; Chatterjee et al., 2001; Buchholzer et al., 2002).

So far, these "presynaptic" effects of hyperforin are its main in vitro effects in the CNS, being measurable at concentrations of 0.1–1 uM. Thus, binding assays gave similar affinity values for dopamine D1 and opioid receptors only, but affinities higher than 2–10 uM for 5HT1A/B/2C/3/5/6/7, D2/3/4/5, neuropeptide-$Y_{1/2}$, sigma, corticotrophin releasing factor-1, GABA-A and benzodiazepine

receptors (Gobbi et al., 2001; Simmen et al., 2001; Butterweck et al., 2002). As indicated above, these concentrations are much higher that found in the rat brain after pharmacologically active doses of SJW exctract or hyperforin (less than 5 nM) (Cervo et al., 2002; Mennini et al., 2002).

These negative results might signify: a) that hyperforin binds to other CNS receptors, not considered in these previous studies or b) that hyperforin acts indirectly on CNS receptors, through a metabolite whose structure is still not known, or by inducing the production of neuromodulators.

Here we will focus on the ex vivo and in vivo studies to determine whether hyperforin or its extracts do actually interfere with monoaminergic neurotransmission in vivo and if this could be responsible for the antidepressant activity. Finally, we will concentrate on the possibility that the antidepressant effects of SJW extract or hyperforin are indirectly mediated by sigma receptors.

Serotoninergic system

Results are conflicting as regards the effect of acute doses of SJW extracts on the serotoninergic system in rodents. Thus, a marked increase of both 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) was reported in rat brain cortex (Calapai et al., 1999). Yu (2000) reported high 5-HIAA and 5-HT levels in mouse hypothalamus and hippocampus but not in the cerebral cortex, where only 5-HIAA increased. Also in mice, (Serdarevic et al., 2001) found a very small increase of whole-brain 5-HIAA, but not 5-HT. Finally, Gobbi et al. (1999) found no significant changes in either 5-HT or 5HIAA after a schedule of treatment active in the forced swimming test. In no instance, therefore, do the effects of SJW extracts resemble the effects of classical 5-HT re-uptake blockers which, after acute or short-term treatment, lower the brain concentrations of 5-HIAA without changing the 5-HT content (Fuller et al., 1988; Caccia et al., 1992).

Another study (Fornal et al., 2001) found no effect of SJW extracts on the firing rate of 5-HT neurons in the cat dorsal raphe, which is inhibited by compounds such as the 5-HT reuptake inhibitors, that increase the synaptic availability of 5-HT. At variance with these results, a ‘‘push-pull superfusion’’ study in the rat locus coeruleus showed that systemic hyperforin induced a lasting (>5 h) and marked (100–200%) increase in the extracellular concentrations of 5-HT, but not 5-HIAA (Kaehler et al., 1999). Although it was suggested that this last effect was a consequence of direct inhibition of the uptake process, indirect effects cannot be excluded.

Panocka et al. (2000) reported that the anti-immobility effect of SJW extracts in the ‘‘forced swimming test’’ was reduced by i.c.v. pre-treatment with 5,7-dihydroxytryptamine, a neurotoxin that markedly depletes brain 5-HT. These findings, however, were difficult to interprete since the toxin alone markedly - though not significantly – reduced the immobility time.

Overall, the scant data available indicates that SJW extracts or hyperforin may affect 5-HT neurotransmission in vivo (at least in the locus coeruleus), although possibly not through a direct interaction with presynaptic 5-HT terminals. We still do not know how this effect is related to the antidepressant activity of SJW.

Dopaminergic and noradrenergic systems

SJW extracts raised diencephalon (but not cortical) DA and NA concentrations in rats, but only at the highest acute oral dose tested (Calapai et al., 1999). Oral administration of the SJW extract caused a slight but significant increase of DA outflow in both the nucleus accumbens and the striatum, as evaluated by in vivo microdialysis (Di Matteo et al., 2000).

Extracellular DA concentrations doubled and there was a transient 50% increase in extracellular NA concentrations using the push-pull perfusion technique after i.p. injection of hyperforin, although the wide variability of these data meant the difference was not statistically significant (Kaehler et al., 1999).

Overall, it would appear that quite high doses of SJW extracts centrally increase DA and NA transmission, an effect possibly mediated by hyperforin. However, it is still not possible to conclude firmly whether these effects are due to a direct interaction of hyperforin on DA and NA nerve endings (through inhibition of their reuptake) or to indirect mechanisms.

The involvement of the dopaminergic system in the pharmacological effects was confirmed by the fact that the effect of the extract in the tail suspension test in mice was antagonised by DL-β-butyrolactone, which reduces the firing of dopaminergic neurons (Butterweck et al., 1997). Moreover, haloperidol (D_2/D_4 and sigma receptor antagonist) and sulpiride (selective D_2/D_3 receptor antagonist) completely antagonized the effects of the extract in the "forced swimming test" in rats (Butterweck et al., 1997). Sulpiride also antagonised the anti-immobility effect of solubilized hypericin (Butterweck et al., 1998) and hyperforin trimethoxybenzoate (Cervo et al., 2004). This suggests that D_2 receptors are involved in SJW's effect on immobility, although it or its components do not bind to D_2 receptors in vitro. In fact, various antidepressant drugs that reportedly have no direct effect on central DA mechanisms enhance the sensitivity of postsynaptic DA receptors in the mesolimbic system by a mechanism that is not known (Garattini and Samanin, 1988).

Sigma receptors

In rats rimcazole (a $sigma_1$ receptor antagonist) counteracts the antidepressant effects of the SJW extract, evaluated with the "forced swimming test" (Panocka et al., 2000). However, binding to sigma receptors was not significantly inhibited by two SJW extracts, or by hyperforin, hyperforin analogues or biapigenin (Gobbi et al., 2001). Hypericin and pseudohypericin inhibited ligand binding to sigma receptors with IC_{50} values of 1.4 μg/mL (Raffa, 1998), although this inhibitory effect of hypericin is partly light-dependent (Gobbi et al., 2001). The hypericin concentration required for these interactions appears to be much higher than the nanomolar plasma concentrations reached in humans after pharmacologically effective doses of SJW extracts (Staffeldt et al., 1994).

In spite of the lack of affinity in vitro, it was recently reported that pre-treatment of rats with pharmacologically active doses of SJW extracts or hyperforin trimethoxybenzoate reduced ligand binding to sigma receptors, measured ex vivo (Pirona et al., 2002, Cervo et al., 2004). The antidepressant-like activity of hyperforin trimethoxybenzoate was completely antagonized by pre-treating rats with BD 1047, a selective $sigma_1$ antagonist (Cervo et al., 2004). These results, together with the observation that agonists at $sigma_1$ receptors are active in antidepressant models in rats (Matsuno et al., 1996), suggest that the SJW extract's antidepressant effect might be mediated by an indirect action on sigma receptors (i.e. the formation of an un identified metabolite or the release of an endogenous ligand).

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