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SPECIAL ISSUE

Helge Frieling · Stefan Bleich

Tranylcypromine

New perspectives on an "old" drug

Abstract The irreversible inhibitor of monoamine oxidase, tranylcypromine, is a potent antidepressant, but its use is limited to special indications due to side effects and dietary restrictions. The antidepressant action of tranylcypromine is not completely explainable by its effects on monoamine oxidase. Tranylcypromine also leads to an increase in brain trace amines, which are believed to play a key role in the pathophysiology of depression. It also affects other pathophysiological pathways associated with depression. Tranylcypromine treatment leads to an up-regulation of $GABA_B$-receptors and modulates the phospholipid metabolism, which is essential for normal brain function. These findings implicate that the efficacy of tranylcypromine as an antidepressant may be due to its multiple actions within the human brain.

Keywords tranylcypromine · mono-aminoxidase · antidepressive action · trace amines · depression

Introduction

Non-selective monoamine oxidase (MAO) inhibitors (MAOI) like tranylcypromine (TCP) or phenelzine (PLZ) have proven to be potent and efficient antidepressants [47]. However, due to side effects and dietary restrictions, their use has been limited to "therapy-resistant depressions" and "atypical depressions" with prominent neurovegetative symptoms [57]. At the introduction of the reversible MAO inhibitor moclobemide (MOC), it was expected that a comparable antidepressive efficacy could be achieved with a favourable security profile [17]. In a recent meta-analysis, it has been shown that MOC is less effective than TCP or PLZ in the treatment of major depression [35]. This difference may not only be explainable by diverse binding-profiles to MAO isoforms since mechanisms of drug action apart from MAO inhibition may contribute to the potency of TCP or PLZ. In the present work, the authors concentrate on possible effects of TCP on other neurochemical systems associated with depression or antidepressive actions.

Dr. H. Frieling, MD (✉) · S. Bleich, MD
Department of Psychiatry and Psychotherapy
Friedrich-Alexander-University of Erlangen-Nuremberg
Schwabachanlage 6
91054 Erlangen, Germany
Tel.: +49-9131/8534-884
Fax: +49-9131/8534-196
E-Mail: helge.frieling@psych.imed.uni-erlangen.de

Pharmacological profile of tranylcypromine

Tranylcyprominehemisulfate (MW: 364.46 g/mol) is a stereoisomeric substance with a structural analogy to amphetamine (Fig. 1). (+)-TCP mainly inhibits MAO while (−)-TCP interacts with monoamine-reuptake and release [54]. Both enantiomers exhibit markedly different pharmacokinetic properties such as plasma levels in humans and clearance rates from rat brains. Until recently, metabolic differences between the two enantiomers have not been investigated [25, 55, 59].

Metabolism

Following oral administration, TCP is rapidly absorbed and has a short elimination half-life of about 2 h in humans [36]. It remains unclear, whether TCP is metabolized via opening of the cyclopropyl ring to amphetamine. Elevated levels of amphetamine and *N*-methylamphetamine have been observed in plasma samples of a patient ingesting 250 mg TCP [62]. Other researchers have been unable to demonstrate such conversion [29, 46]. Recently, it has been shown that opening of the cyclopropyl ring does not occur at usual doses of TCP [51]. Biotransformation of TCP seems to follow diverse ways: *N*-acetyl-TCP has been

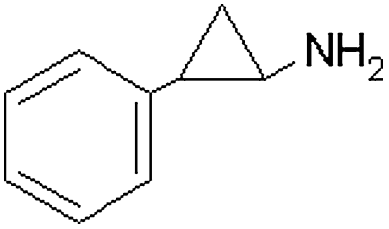

Fig. 1 Chemical structure of tranylcypromine

found in brain and urine of TCP-treated rats [12, 31] as well as 4-Hydroxy-TCP, the latter also being an inhibitor of MAO-A and B [3, 5]. TCP and its metabolites are renally excreted.

Effects on neurotransmitter amines

The basic principle of the antidepressive action of TCP is an elevation of the catecholamines norepinephrine (NE) and dopamine (DA) and the indolealkylamine 5-hydroxytryptamine (5-HT, serotonin) by inhibiting the main enzymes of their degradation, the monoamine-oxidases A and B. However, treatment with TCP leads to an increase of activity of the semicarbazide sensitive amine oxidase (SSAO), another amine oxidase that metabolises NE, DA and 5-HT in different tissues, at least in rat hearts [18, 19]. Alterations in SSAO activity have been reported to be present in different psychiatric disorders [63]. Recently, we have found significantly lower plasma levels of SSAO in depressed patients when compared with healthy controls [65]. MAO and SSAO inhibition also leads to a marked increase of brain amines as tyramine (TYR), tryptamine (TRY), β-phenylethylamine (β-PEA) and octopamine (OCT), which are termed "trace amines" (TA) because of their low absolute concentrations in the brain relative to NE, DA or 5-HT. TAs can exert pharmacological effects: they can affect release or uptake of catecholamines and 5-HT at nerve endings [4, 44], and they seem to act as neuromodulators directly acting on catecholamine- or 5-HT-receptors [30, 43]. The interest in TA is mounting since the discovery of G-protein-coupled receptors for trace amines [8] and led to a "rebirth" of the PEA hypothesis of affective disorders. Briefly, a deficit of PEA that is postulated to be responsible for sustaining mood, physical energy and attention, or a deficit of PEA-turnover is proposed by several groups to be a causal factor for endogenous depression whereas an excess may lead to mania [14, 26]. Interestingly, PEA and phenylacetic acid (PAA), the main metabolite of PEA are metabolites of phenelzine (PLZ), another MAOI that is in clinical use as antidepressant [2]. TCP treatment leads to an increase of brain trace amines. However, the measured increase of PEA after MAO inhibition was not significantly correlated with improvement of depression [34]. Besides PEA, also TRY is discussed to be involved in the development of depression. Treatment with TCP and PLZ decreases the density of ^{3}H-TRY-binding sites in rat brains. High doses of TCP lead to down-regulation of TCY-receptors in the hippocampus and striatum of rats [21, 39]. However, the clinical significance of these findings needs to be further clarified.

Trace amines and their receptors are discussed to be involved in different neuropsychiatric disorders such as psychosis and attention deficit and hyperkinetic disorder (reviewed in [9]), for some of those disorders casuistic data exist postulating a therapeutic effect of TCP.

Effects on receptors for amines and amino acids

Mainly the elevation of catecholamines and 5-HT seems to lead to changes in several pre- and postsynaptic receptors. Chronic administration of TCP lead to a down-regulation of β_1- and β_2-adrenoceptors in the rat brain cortex and other regions of the rat brain [20, 37, 38, 40, 52]. Some data exist proposing also a down-regulation of α_1- and α_2-receptors after chronic treatment with TCP in the rat brain [23]. Additionally, a decrease of 5-HT2-receptors was found after administration of high and low doses of TCP in rats [13, 21]. Furthermore, after chronic administration of TCP, a down-regulation of dopaminergic D_1 and D_2 receptors in the rat striatum was found [41].

γ-Amino-butyric-acid is one of the neurotransmitters that have received considerable attention during the last years for their possible involvement in affective disorders. Studies using animal models of depression, radioligand binding and functional studies in rodent brain tissue and neuroendocrine challenge investigations implicate GABA in the pathophysiology of depression. However, these studies are not without conflicting findings [33, 58]. Chronic administration of TCP and some other antidepressants (PLZ, desipramine, fluoxetine) lead to a selectively increased expression of the $GABA_{B(1a)}$ subunit of the receptor in rats hippocampus. Only TCP leads also to an increase of the expression of $GABA_{B(2)}$ subunit. Treatment of rats with TCP significantly enhanced the response to baclofen, a $GABA_B$-receptor agonist, in the hippocampal tissue and leads to an increase of locomotor activity after amphetamine administration [49, 50].

Effects on enzymes other than MAO

Effects on cytochrome enzymes

The concomitant use of TCP and other drugs is restricted not only because of the elevated risk for

hypertensive crisis or central serotonergic syndrome but also because of some possible interactions concerning cytochrome P 450 based drug degradation. Tranylcypromine is a potent inhibitor of CYP2A6 [15], CYP2E1 and, to a lesser extent, CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP2D6. The effectiviy of CYP inhibition depends on the amino group of TCP. The non-amine homologue of TCP, cyclopropylbenzene, is a much less potent inhibitor of CYP1A2, CYP2A6, CYP2C19 and CYP2E1 activities and did not inhibit CYP2C9, CYP2D6 and CYP3A4 [56]. However, the inhibitory effects of TCP on the "usual suspects" for CYP-based drug–drug interaction, CYP2C9, CYP2C19 and CYP3A4 are not considered clinically relevant. During high-dose TCP therapy or in poor metabolizers of CYP2C19 substrates, clinically relevant interaction may occur [48].

CYP2A6 is the principle enzyme metabolizing nicotine to its inactive metabolite cotinine. It has been hypothesized that TCP may be useful to decrease smoking by inhibiting nicotine metabolism [64]. It has been well documented that the rate of cigarette smoking among psychiatric patient (e.g. depressed [10, 11, 16] or schizophrenia [60]) is significantly higher than in the general population. Smoking may reflect an attempt of self-medication [32], maybe by cigarette smoke mediated MAO inhibition [7]. The inhibitory effect of TCP on nicotine metabolism possibly contributes to its antidepressive effects. However, the relation between smoke, depression, MAO and TCP remains to be further clarified.

Effects on phospholipids and lipid-mediators

Recently, abnormalities in the metabolism of phospholipids have been implicated in the pathophysiology of depressive disorders. Phospholipids are essential for neuronal and synaptic structures and play key roles in the signal transduction response to different neurotransmitters [6]. Phospholipid derived mediators like prostaglandins, leukotrienes and thromboxanes are fundamental for many functions of the organism, e.g. the immune system. Especially, the role of poly-unsaturated fatty acids (PUFA) like omega-3 ($\omega 3$) or omega-6 ($\omega 6$) fatty acids and the $\omega 3/\omega 6$-ratio in the plasma membrane and lipid mediators has been widely investigated [24]. In depressed patients, an imbalance in PUFAs has been found with an excess of $\omega 6$ acids like arachidonic acid (AA) and a deficiency of $\omega 3$ fatty acids, such as eicosapentaenoic or docosahexaenoic acid. It was postulated that overactivity of different enzymes of the arachidonic cascade, like phospholipase A_2 (PLA_2) or coenzyme-A-independent transaminase (CoAIT) was underlying this imbalance, as diet did not seem to be its main cause [28]. CoAIT is of special interest, as this enzyme specifically affects only AA but not $\omega 3$-fatty acids [61]. TCP is known

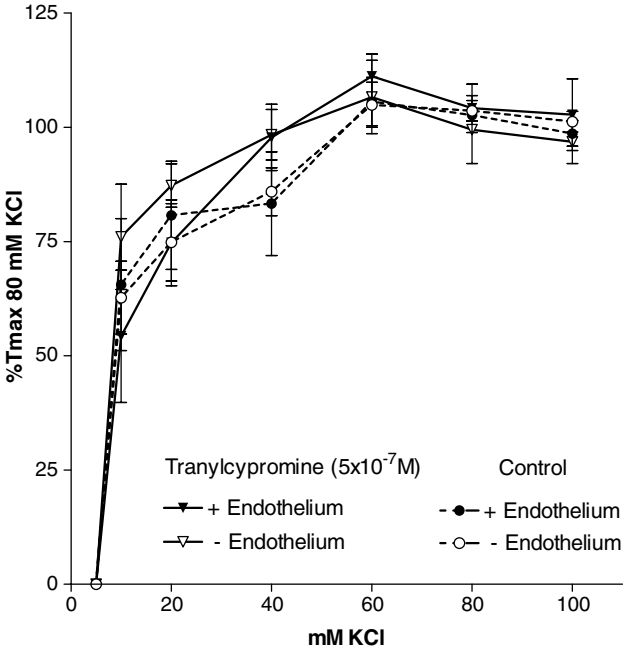

Fig. 2 Dose–response curve of KCl induced vascular contraction after TCP incubation. Cumulative concentrations of KCl (5–100 mM) were tested for their vasoconstrictory action in an isometric preparation of rat thoracic aorta with and without endothelium ($n = 4$, each). No difference was found in preparations pre-incubated in 5×10^{-7} M tranylcypromine (20 min) as compared to controls

to inhibit the release of AA from bradykinin-stimulated endothelial cells. It remains unclear, if this effect is due to PLA inhibition or if another enzyme is involved. It could be hypothesized that TCP inhibits CoAIT and therefore attenuates the $\omega 3/\omega 6$ imbalance by reducing the AA release. It is well known that lipid mediators derived from $\omega 3$ fatty acids are more potent antiinflammatory and less potent proinflammatory agents than those derived from $\omega 6$ fatty acids and may therefore excert positive effects on immune disturbances observed during depression [53]. Other effective antidepressive therapies like electroconvulsive therapy or lithium salts also affect the arachidonic cascade making the modulation of phospholipids an interesting target for novel antidepressants [1, 45].

TCP does not only affect AA release but also inhibits the prostacyclin synthase and therefore decreases the prostacyclin (PGI_2) production [27]. Until recently, this property of TCP has not found attention in psychiatric research. PGI_2 is one of the prominent endothelium derived vasodilating mediators [22, 42]. It is, therefore, surprising that TCP does neither have vasorelaxing nor vasoconstricting properties in vitro (Figs. 2 and 3), unlike other antidepressants (i.e. Amitriptyline) that lead to full relaxation of smooth muscles in vitro. This finding is of special interest, as both agents lead to orthostatic hypotension as one of their main side-effects. In the case of TCP, it is un-

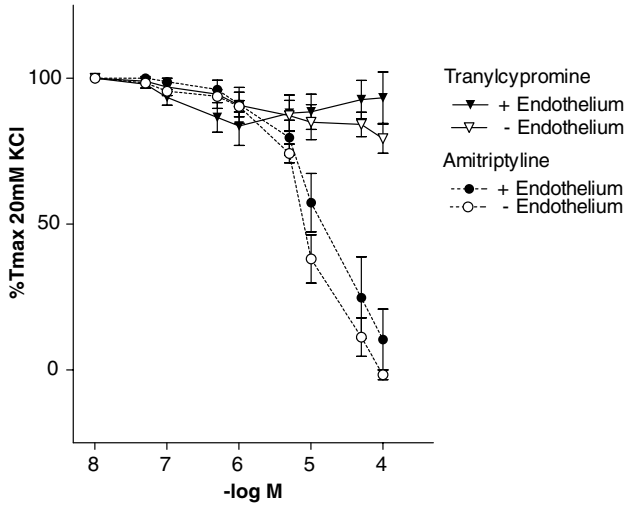

Fig. 3 Relaxing effects of amitriptyline but not tranylcypromine on KCl induced vascular tone. The effects of cumulative concentrations (10 nM–100 μM) of amitriptyline and tranylcypromine on tension elicited by 20 mM KCl were examined in isometric preparations of rat thoracic aorta with and without endothelium ($n = 4$, each). No relaxing effects were found for tranylcypromine, while cumulative concentrations of amitriptyline lead to complete relaxation of the vessel

likely to be mediated by peripheral effects of the drug, even though TCP interacts with different vasomotor controlling pathways.

Summary

Tranylcypromine is an efficient antidepressant. It does not only affect monoamine neurotransmitters by inhibiting the main enzymes of their degradation, MAO A and B, but is also implicated in several other pathophysiologic pathways, which have been associated with depression. TCP increases brain levels of trace amines, up-regulates $GABA_B$-receptors and interferes with a variety of cytochrome P450 enzymes. TCP inhibits the release of arachidonic acid and prostacyclin, implicating diverse effects on inflammation, neuroplasticity and neurodegeneration. It is, therefore, not a selective inhibitor of monoaminoxidase, as the description MAOI may suggest. TCP is a somewhat "dirty drug" as it has a broad variety of effects. The most effective antidepressive treatments, however, affect more than one pathophysiological pathway. For further investigations in new antidepressants, a guideline may be "the dirtier the better". Today, however, many of these "dirty drugs" come along with an unfavourable security profile or like TCP, drastic dietary restriction limiting there clinical use to special indications. Profound understanding of the pharmacologic profile of drugs like TCP may lead to more efficient and safe antidepressants in the future.

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