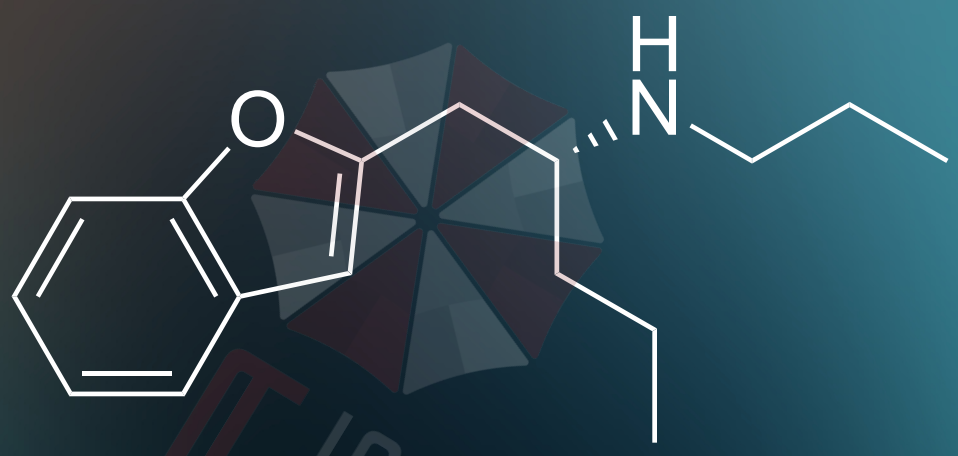

Preclinical Insights into BPAP: A Compound Enhancing Monoamine Release in the Rat Brain

History

(–)-Benzofuranyl-propylaminopentane (BPAP; also known as FPFS- 1169) is a compound first described in 1999 by a Hungarian research group.[1,2] It enhances the activity of the monoamine neurotransmitters noradrenalin, dopamine and serotonin in certain brain areas and it can generally be considered to produce stimulant effects. It is part of the group of monoaminergic activity enhancers (MAE), which increase the amount of monoamines secreted into the synaptic cleft, but do not lead to a continuous release without proper stimulation by a neuron as is the case with most amphetamines. The drug selegiline is an example for a clinically approved MAE and is used to treat depression and Parkinson's disease. The prevailing idea at its time of discovery for BPAP was to be used for the same conditions. Selegiline and BPAP were both investigated by the same Hungarian psychopharmacologist named József Knoll. He also promoted the concept of MAE as antiaging compounds and wrote several articles about the subject.[3]

BPAP is a close relative of 1-Phenyl-2-propylaminopentane (PPAP), which has a similar activity profile compared to BPAP, it does not act on the serotonin system and generally has a lower potency.[2]

Chemically, BPAP is also closely related to the naturally occurring substance tryptamine, which is known to act as a serotonin receptor agonist as well.

The synthesis of BPAP has been published as far back as 2001.[4,5]

Preclinical Data

Radical scavenging

Radicals in biosystems are potentially dangerous intermediate side products of regular metabolic processes. Radicals have been linked to the aging process and some diseases. Radical scavengers are molecules which are able to neutralize the radicals and hence their negative impact on the body. A theoretical study has found that BPAP is an effective radical scavenger due to its molecular structure.[6] This is true for many compounds, and hence it is not clear of the anti aging benefits of BPAP are connected to this property of BPAP.[7]

Mechanism of Action

BPAP significantly enhanced the impulse propagation mediated release of noradrenaline and dopamine in 0.18 µmol/l

concentration and in 36 nmol/l concentration the release of serotonin from the isolated brain stem of rats. The amount of catechol amines and serotonin released from isolated discrete rat brain regions enhanced significantly in the presence of 10−12- 10−14 mol/l BPAP.[2] The protein TAAR1 was confirmed to be involved in the signaling cascade of BPAP, which is also the case in similar drugs.[7]

In ex vivo experiments, when an isolated brain region was soaked in an organ bath containing BPAP, the release of noradrenaline was significantly enhanced at 10−16 M BPAP, reached a peak effect at 10−13 M, but 10−10 M BPAP was ineffective. A significant enhancer effect was detected also in the high concentration range from 10−8 M, the peak effect was reached at 10−6 M concentration and 10−5 M BPAP was ineffective. BPAP enhanced in the low concentration range the performance of dopaminergic and serotoninergic neurons with a peak effect at 10−13 and 10−12 M concentration, respectively. The results suggest that high and low affinity 'enhancer' receptors may exist in the brain.[8]

BPAP also inhibited the noradrenaline release usually induced by the compound tyramine. Thus, BPAP may block tyramine-induced adverse effects such as hypertensive crisis. It was also found in the same study that BPAP is not only catecholaminergic and serotonergic activity enhancer, but also a norepinephrine and dopamine reuptake inhibitor (NDRI) and a weak serotonin reuptake inhibitor (SRI).[9]

Expermientally, these properties lead to an increased movement urge in rats when administered with 1-3 mg/kg of BPAP. This dose was also able to counter the movement depressing properties of the drug reserpine. Furthermore, although antiparkinsonian agents, such as apomorphine and amantadine, failed to improve reserpine-induced ptosis, BPAP HCl significantly improved ptosis.[10],[11]

Induced learning & depression

Tetrabenazine is a drug that has the reverse effect of MAEs in the brain, slowing down the release of monoamines. Applied in high enough doses, it can severely hinder learning in rats. Substances that enhance the impulse-propagation-mediated release of catecholamines in the brain can antagonize tetrabenazine. The prevention of tetrabenazine- induced learning depression by the simultaneous administration of BPAP was demonstrated. In antagonizing the effect of tetrabenazine, BPAP was found to be 130 times more potent than selegiline.[12],[13],[10]

BPAP has also been theorized to be a suitable compound in the treatment of depression. A study cites its peculiar pharmacological profile, the high potency and unusual safeness and tolerability of BPAP which gives reason to hope that this compound by itself and in combination with uptake inhibitors may improve the effectiveness of drug therapy in major depression and diminish the number of therapy resistant cases.1

BPAP was able to improve to regulate social and sexual behaviour in rats that had been subjected to highly stressful circumstances. This improvement was also seen if a depression of regular behaviour was induced by dopamine receptor antagonists. These results indicate that BPAP could be used to effectively treat depressive disorders in humans as well.[14]

There is also evidence from an animal model that BPAP could be used as an agent to manage drug withdrawal from amphetamines and potentially other forms of recreational drugs.[15]

Neuroprotection

Like other MAEs, BPAP has been observed to protect neural cells from apoptosis, hence keeping the networks of neurons intact. In rats BPAP significantly enhanced the activity of the catecholaminergic and serotoninergic neurons in the brain 30 min after acute injection of 0.1 mg kgs.c. [8]

BPAP was also found to protect neurons in the presence of a neurotoxin, which usually leads to cell death due to the dissolution of the mitochondria. If BPAP was present, the mitochondria stayed intact and the toxicity of the neurotoxin was mitigated.8 BPAP also protected cultured hippocampal neurons from the neurotoxic effect of β-amyloid in 10−14 M concentration.[16] The protective effect of BPAP on neurons was also observed when the cells were placed into foreign

environments where the neurons usually undergo cell death.[17]

A very interesting study has investigated the effect of selegiline and BPAP on the life expectance of rats. The result showed both substances at low doses (0.05 mg/kg BPAP) led to a significantly longer lifespan in both cases. The animals lived several months longer than their non-treated counterparts (around 10% extension of lifespan). Animals of the same age also had a better results in learning test when treated with selegiline or BPAP.[18]

Cancer

It was discovered that it is also effective against certain types of experimental cancers, showing the most promising results in case of lung cancer. Data showed that BPAP in low doses (0,0001 mg/kg per day) and high doses (0,005 mg/kg per day) halted the growth of the tumor cells. In addition, low dose BPAP treatment had a beneficial effect on bodyweight suggesting that the compound at least in part is able to compensate the cancer-related wasting.[19]

Metabolism

In rats, BPAP is mostly eliminated through the urine, but also in the feces by a smaller amount. The biological half-life is roughly 5,6 hours, hence almost all BPAP is eliminated within 3 days after administration.[20]

Conclusion

BPAP is a close relative to clinical drugs currently in use, most notably the monoamine oxidase inhibitor selegiline. However, BPAP has a number of additional pharmacological effects on neurotransmitter systems. It influences the transmitters noradrenaline, dopamine and serotonin and generally leads to an increase in the activity of the associated neurons. Through this mechanism, it could potentially be studied and researched in depression and Parkinson's disease.

Additionally, it has been shown to increase the survivability of neurons and one study has even demonstrated an overall prolonging effect on the lifespan of rats.

Even though there is a substantial amount of interesting preclinical data, there are no reports on clinical trials with BPAP. Hence, metabolic properties have not been investigated either.

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