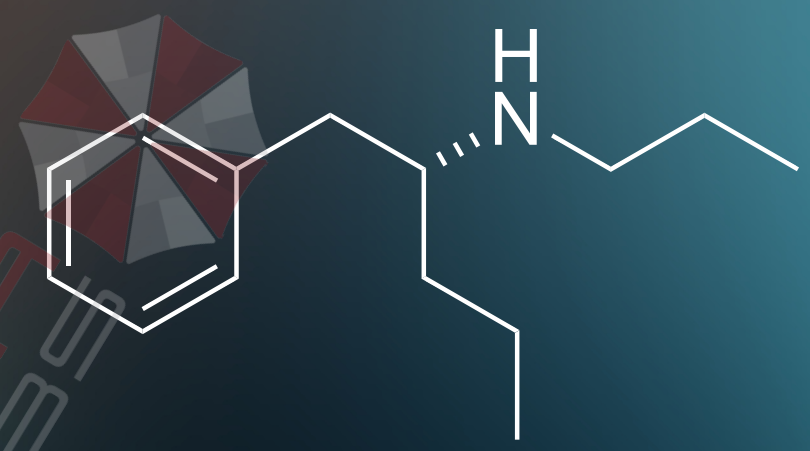

Phenylpropylaminopentane - The Role of PPAP in Modulating Neurotransmitter

History

Phenylpropylaminopentane (PPAP), also known as (-)-PPAP and N,α-dipropylphenethylamine was first patented in 1993 (US 5220068) as a psychostimulant. Structurally, it is related to the endogenous neurotransmitters dopamine, noradrenaline and adrenalin. It is a member of a group of amphetamine analogs with a softer profile compared to compounds like methylamphetamine. In contrast to such compounds, which release neurotransmitters into the synaptic cleft in an indiscriminate manner and lead to a general stimulation of the sympathetic nervous system, PPAP does only increase the neurotransmitter release if an neuron is stimulated under regular circumstances. Due to this, PPAP also referred to as a catecholaminergic activity enhancer (CAE). Other members of this group with similar structure & properties have been proposed as possible agents to slow down ageing processes of the brain.[1] Whether this can also be expected from PPAP, is not sufficiently shown at the present date.

Preclinical Data

A comparative study evaluated the effects of PPAP and deprenyl, another amphetamine with the ability to block the breakdown of neurotransmitters, which is a property that PPAP does not possess. In rat brain neurons, both substances act as potent stimulants of neurotransmitter release in many areas of the brain. [2] In a similar study on immune cells, PPAP was able to raise the serotonin levels 30 mins after initial treatment and after 3 weeks of continuous treatment. In contrast to this deprenyl did not change serotonin levels in 30 minute timeframe while it led to a drop of serotonin after 3 weeks. These results indicate that PPAP and deprenyl have a different mode of action and secondary effects, even though both are known to increase the activity of the sympathetic nervous system.[3]

By itself, PPAP increases the urge to move in rats at doses starting at 2 mg/kg, but it can also inhibit the effect of other amphetamines at higher doses of PPAP (50 mg/kg). It is also able to strengthen motivation and the ability to learn like other amphetamines. However, it has a much broader range for effective dosing, since the administration of amphetamines quickly shows a reduced ability to learn and more serious side effects if ingested above the ideal dose. Hence, PPAP is a much more promising candidate if such effects are desired in a broader setting.[4] PPAP can also reduce the

depression like symptoms in rats which are evicted by substance tetrabenazine at a PPAP dose of 5 mg/kg.[5] However, another study on rats reports a much higher required dose of PPAP to antagonize the effects of tetrabenazine (1-5 mg/kg PPAP).[6] Tetrabenazine depletes the storages of adrenalin, noradrenalin and dopamine in the brain, which is known to lead to a depressive state in humans characterized by a severe lack of motivation.

In addition to its effects on the release of neurotransmitters in the sympathetic nervous system, PPAP was also found to bind to sigma receptors with a high affinity (24 nM). These receptors play a role in a large variety of physiological processes, including learning and cell proliferation.[7]

Conclusion

There are only few studies in animals reporting beneficial effects on depression, movement enhancement and learning in rats. These indicate PPAP could have a promising effect to dose ratio and lower risks of overdosing compared to other drugs which increase the release of catecholaminergic neurotransmitters in the brain. However, there is no toxicological data and no reported studies in which PPAP was administered to humans. More studies are needed to confirm or disprove the applicability of PPAP in humans for any purpose.

References

[1] Knoll J. *How Selegiline ((-)-Deprenyl) Slows Brain Aging*. BENTHAM SCIENCE PUBLISHERS.

[2] Knoll J, Miklya I, Knoll B, Markó R, Kelemen K. (-)Deprenyl and (-)1-phenyl-2- propylaminopentane, (-)PPAP, act primarily as potent stimulants of action potential-transmitter release coupling in the catecholaminergic neurons. *Life Sci.* **1996**;58:817–827. doi: 10.1016/0024-3205(96)00014-8.

[3] Csaba G, Kovács P, Pállinger E. Acute and delayed effect of (-) deprenyl and (-) 1-phenyl-2- propylaminopentane (PPAP) on the serotonin content of peritoneal cells (white blood cells and mast cells). *Cell Biochem Funct.* **2006**;24:49–53. doi: 10.1002/cbf.1183.

[4] Knoll J, Knoll B, Török Z, Timár J, Yasar S. The pharmacology of 1-phenyl-2-propylamino-pentane (PPAP), a deprenyl-derived new spectrum psychostimulant. *Arch Int Pharmacodyn Ther*. **1992**;316:5–29.

[5] Knoll J, Yoneda F, Knoll B, Ohde H, Miklya I. (-)1-(Benzofuran-2-yl)-2-propylaminopentane, (-)BPAP, a selective enhancer of the impulse propagation mediated release of catecholamines and serotonin in the brain. *Br J Pharmacol*. **1999**;128:1723–1732. doi: 10.1038/sj.bjp.0702995.

[6] Knoll J, Miklya I, Knoll B, Yasusa T, Shimazu S, Yoneda F. 1-(Benzofuran-2-yl)-2-(3,3,3- trifluoropropyl)aminopentane HCl, 3-F-BPAP, antagonizes the enhancer effect of (-)-BPAP in the shuttle box and leaves the effect of (-)-deprenyl unchanged. *Life Sci.* **2002**;71:1975–1984. doi: 10.1016/s0024-3205(02)01968-9.

[7] Glennon RA, Battaglia G, Smith JD. (-)PPAP: a new and selective ligand for sigma binding sites. *Pharmacol Biochem Behav*. **1990**;37:557–559. doi: 10.1016/0091-3057(90)90027-