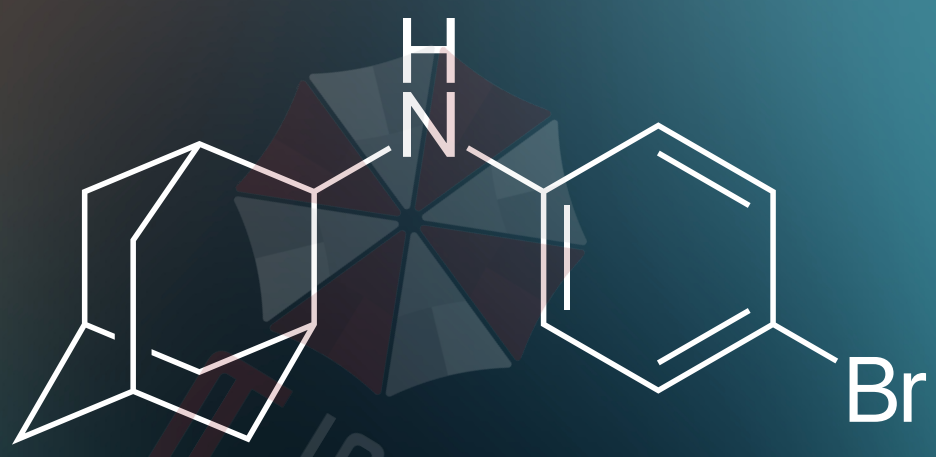

Bromantane
A Russian Innovation in Neuropsychopharmacology

Bromantane acts as a central nervous system stimulant and also has anti- anxiety effects. Its exact mechanism of action is not known, although it is thought to influence neuronal activity through dopaminergic and serotonergic neurotransmission.

It is a derivative of the compound amantadine, which is used to treat infections with the influenza virus as well as symptoms of Parkinson's disease. Amantadine is approved in the US and in the EU, while bromantane is not.

Bromantane is however medically approved for treatment in Russia under the name "Ladasten" to treat "neurasthenia", which is not a commonly accepted diagnosis in most countries anymore. It describes a state of general weakness and dizziness, maybe better represented by the term "mental fatigue".

Bromantane is included in the prohibited list of the World Anti-Doping Agency.

Possible Mechanism of Action

Bromantane was reported to suppress the uptake of dopamine (and, to a greater extent, serotonin) in rat brain synapses, while not affecting noradrenaline. This study claims that Bromantane increases the release of dopamine in some brain areas and behaves as an agonist of the dopamine receptors and antagonist of the m- and n-acetylcholine receptors.[1] However, a later study has claimed that there is direct influence on the dopamine receptors.[2] In that particular study, the influence of bromantane and sydnocarb (a dopamine reuptake inhibitor) on dopamine and serotonin receptors and the biosynthesis and re-uptake of dopamine and serotonin has been subject of a study. As mentioned, it was established that both drugs do not produce any direct effects on dopamine receptors or serotonin receptors. Bromantane in a single dose of 50 mg/kg (intraperitoneally injected) stimulated dopamine biosynthesis and release, without any influence on serotonin formation. On the contrary, sydnocarb (17.5 mg/kg) decreased the level of serotonin synthesis, while not affecting the biosynthesis of dopamine. Both bromantane and sydnocarb inhibited the active transport of dopamine in synapses at IC50 = 3.56 μM and 28.66 nM, respectively, but failed to influence the serotonin re-uptake.[2]

The main effect of bromantane is reported to be its dopamine-positive activity and secondarily, a more complicated influence on the serotoninergic system. The

central noradrenergic effect of the drug is less expressed, as it can only influence this system at high concentrations (more than 500 µM). The drug (1- 50 mg/kg, intravenously) has no effect on neuro-muscular transmission in cats and in higher doses (30-600 mg/kg) inhibits to a certain degree the central effects of nicotine.[3]

Animal Studies

In rats, it was demonstrated that bromantane induces a pronounced and prolonged (8 h) increase in the release of dopamine. Interestingly, Tetrodotoxin (1µM), a sodium channel blocker, was shown to partially inhibit the bromantane-induced release of dopamine.[4]

The effects of bromantane and reference product imipramine (10 mg/kg) on the release of various cytokines in a depression model of mice were studied. Bromantane was injected 5 times in doses of 30 and 50 mg/kg. Behavioral disturbances and significant increase in the concentration of pro-inflammatory cytokines and was more potent than imipramine in that effect.[5]

In another study, a single administration of bromantane (50 mg/kg, oral) was shown to influence dopamine, noradrenalin and adrenalin metabolism by increasing the biosynthesis of dopamine. The same study also suggested that bromantane induces reinforcement of short-term memory via protein synthesis and dopamine dependent mechanisms.[6]

Bromantane (30 mg/kg intraperitoneally for 5 days) in mice also seems to influence the function of the immune system. When test mice were stressed for 30 days, their immune system parameters worsened due to the chronic stress. Administration of bromantane had a normalizing effect on the immune system, which in some cases even returned to the levels of control animals which were not subjected to chronic stress.[7]

Further results of experiments on rats showed that bromantane affects the sexual behavior and pairing activity. In short term (3 days) and long-term (up to 2 months) experiments with bromantane (30 and 300 mg/kg, oral) the sexual activity of test animals was increased. The observed effects are probably related to the dopamine-positive action of bromantane.[8]

A long-term study investigated the effects of bromantane administration on the pups of reproducing rats. Only the parents received bromantane orally daily in doses of 30, 150, and 600 mg/kg: females received the drug for 15 days (2.5 estrous cycles), males for 60 days (whole cycle of spermatogenesis). According to the results of the investigation, bromantane produced a late-term effect on the formation and development of the offspring. The mean weight of the newborns in the first week was significantly higher than the weight of the controls. After that the growth in body weight was insignificantly slower. The results of this study showed an insignificant increase in the rate of maturation of the sensorimotor reflexes and physical parameters of the young experimental rats. Behavioral changes were also noted. The authors believe that bromantane has an effect on the prolactin levels in females. The deficiency in this hormone in the early period of postnatal development affects the neurochemical organization of the brain, involving in this case also the mechanisms of sexual differentiation of the brain and, as a consequence, the somatic and sexual development of the progeny. Whether this effect is transferable to humans is not clear, but likely.[9]

The expression of 588 genes in rat brain cells in response to a single administration of bromantane, was analyzed in a further study. The analysis of demonstrated that bromantane alters the expression of 12 genes in the rat brain. The GAT3 and CARBH genes are presumed to be pharmacologically important targets of bromantane. The changes in their activity explain the mechanisms of the anxiolytic and mood-stabilizing effects of the drug. Bromantane has been shown to induce the genes whose products are involved in various signal pathways, as well as the genes of cytoskeletal proteins, synaptic proteins, and enzymes. The proteins encoded by these genes are presumably involved in compensatory and/or neuroplastic adaptations to the effects of bromantane.[10] Bromantane was shown to influence the epigenetic expression of some DNA sequences.[11]

The effect of bromantane (50 mg/kg) on the activity of protein

kinase C (PKC)- which is an important mediator in many signal cascades-was studied depending on the duration of drug action. In the initial stage of the drug action, the PKC activity in the cytosol fraction of rat brain proteins exhibits a more than twofold increase. It is concluded that the pharmacological activity of bromantane is related to activation of PKC in rat brain cells. [12]

Toxicity

Bromantane introduced to experimental animals at a dose of acute poisoning (> 300 mg/kg) gives rise to sedative effects, irregular respiration, hypersalivation, diarrhea, and reduced rectal temperature; prolonged administration led to a reversible dose-dependent decrease in heart rhythm, reduced motor activity, moderate neutrophilia and lymphocytosis, increased content of erythrocytes and protein in the blood plasma, and decreased liver parameters.1

The oral administration of bromantane for two months on a toxic dose level produced a sex-dependent action upon rats: the effective (30 mg/kg), intermediate (150 mg/kg), and toxic (600 mg/kg) doses reduced the motor activity. In the initial stage of treatment, bromantane causes hypothermia; in the second month, this effect is replaced by slight hyperthermia. Prolonged administration of a large dose of bromantane oppressed food uptake and slightly increased drink uptake. The two-month treatment did not lead to the development of tolerance with respect to the optimizing drug action upon the physical and operant capacity.[13]

A further toxicity focused study found bromantane in doses of 30-300 mg/kg stimulated and in doses of 600-9600 mg/kg suppressed regular behavioral activity. Spontaneous motor activity increased after single treatment with bromantane in doses of 30-300 mg/kg, did not change after treatment in doses of 600 mg/kg, and was inhibited after treatment in doses above 600 mg/kg. In doses of 300-600 mg/kg the drug reduced pain sensitivity threshold and in doses above 600 mg/kg elevated the pain threshold and tactile sensitivity and reaction to knock. Bromantane induced widening of the pupils in all studied doses. In doses above 5 g/kg bromantane slightly increased respiration rate and depth. In some animals bromantane in high doses induced regurgitation, diarrhea, and polyuria. Rectal temperature decreased by 0.5-1°C after virtually all doses. Behavioral effects of bromantane in doses of 30 and 600 mg/kg were associated with stimulation of the central dopamine and suppression of muscarinic and nicotinic cholinergic structures. This study suggests that at doses higher than 300 mg/kg in rats, many effects reverse, indicating that dosing is crucial to achieve the desired effects.[14]

Clinical Studies

An aim of a randomized blind study was to assess therapeutic efficacy and safety of bromantane used as an antiasthenic drug in patients diagnosed with neurasthenia. Tasks of the study included the investigation of characteristics of therapeutic actions, efficacy of the drug comparing to placebo, possible side-effects and probability of the development of withdrawal syndromes. The study included bromantane and placebo treatment during 28 days and a final 1-week period of receiving placebo. Standardized objective and subjective methods of mental state evaluation in patients were administered. The results obtained suggest that a combination of psychostimulant and anxiolytic actions. It has been found that bromantane is superior in the rate and degree of reduction of main symptoms of asthenic syndrome compared to placebo. The absence of "withdrawal syndrome" after the drug withdrawal reveals the lack of addictive potential in this drug. [15]

A further study was carried out in 28 clinical centers of Russia. All 728 included patients suffered from asthenic disorders. The duration of treatment with bromantane in daily dose from 50 to 100 mg was 28 days. The antiasthenic effect of bromantane was seen on day 3 and remained during one month after the withdrawal of therapy. The authors determined clinical efficacy of bromantane in regard to anxiety-depressive spectrum disorders, autonomic dystonia and sleep disorders. Bromantane therapy led to the significant increase of quality of life, which was seen not only after the end of

therapy, but after the withdrawal of the drug. These results suggest the stability of the therapeutic effect achieved. Adverse effects were observed only in 3% of patients, the therapy was discontinued in 0.8%. No serious adverse effects were found. In conclusion, the efficacy of bromantane was shown in its antiasthenic, anxiolytic, autonomic nervous system stabilizing properties, the normalization of sleep-awake cycle and the increase of quality of life. The assessment of the authors was that bromantane in daily dose from 50 to 100 mg is a highly effective, well-tolerated and safety drug with a wide spectrum of clinical effects. Therefore, this drug could be recommended for treatment of asthenic disorders in neurological practice.[16]

In a smaller scale study, 30 russian veterans of the soviet-afghan war with early forms of chronic brain ischemia and manifestations of psychogenic asthenic syndrome were treated. Bromantane, at a dose of 50 mg 2 times daily causes a variety of symptoms. As previously observed in animal models, an immune system enhancing effect was found. Furthermore, anti- inflammatory activity associated with reduced functional activity of macrophages; effects in blood vessel diameter action expressed as normalized balance of and vasoactive factors (nitric oxide, endothelin-1) were reported. In total the quality of this study was low due to the small sample size and the variety of reported outcomes.[17]

Conclusion

Bromantane acts in the brain and seems to influence the dopamine metabolism primarily, although the exact mechanism of action is not fully understood. The main effects are reported to be overall stimulating and anxiolytic, while positive effects on the immune system were also reported.

The effective clinical dose for humans is 50-100 mg per day, taken orally. At higher doses, the positive effects of the drug can reverse, meaning that an increasing dose of bromantane in order to achieve a stronger effect is likely counter-productive. In addition, toxic effects can be felt at higher doses as well, including a decreased heart-rhythm, hypothermia and suppressed appetite. Doses of over 1 g/day in humans are likely to produce acute toxic effects, based on animal experiments.

In total, there is a solid amount of animal studies published, but only a low number of clinical trials. In addition, almost all literature originates from a few russian groups, which calls the overall objectivity of these studies into question. In addition, the clinical trials focused on diseases which are hard to grasp as a particular physical problem, which complicates the decision at what time it is advisable to use bromantane.

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