The Pharmacology of Actoprotectors: Practical Application for Improvement of Mental and Physical Performance

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Abstract

Actoprotectors are preparations that enhance body stability against physical loads without increasing oxygen consumption or heat production. Or, in short, actoprotectors are synthetic adaptogens with a significant capacity to improve physical performance. This paper explores the history of actoprotectors' development, their pharmacological properties, mechanism of action, and practical application to the improvement of mental and physical performance. A brief summary of the clinico-pharmacological characteristics of the main representatives of this class (bemilin and bromantane) is provided. Some other synthesized compounds, and even natural ones such as ginseng, also are regarded as potential actoprotectors, and these are treated herein as well. Actoprotectors, owing to their wide-ranging pharmacological activities, high efficiency and safety, can be applied under either normal or extreme conditions.

Key Words: Actoprotector, Bemilin, Bromantane, Mental work capacity, Asthenia

Investigations into a new class of pharmacologically active substances for improvement of physical and mental efficiency in humans, namely actoprotectors, were carried out under Professor Vladimir Vinogradov at the Military Medical Academy (then Leningrad, USSR; now, St. Petersburg, Russia)'s Department of Pharmacology throughout the 1970s. This work resulted in the development of the first and most commonly used actoprotector, bemilin (chemical structure: 2-ethylbenzimidazole hydrobromide, (Fig. 1A); English-language literature: "bemithil", "bemithyl" or "bemethyl"; also known as "bemactor" and "metaprot" in later publications). This achievement earned Professor Vinogradov and his research team the State Prize of the USSR. Other actoprotectors subsequently were formulated as well, the most important of which, from the practical point of view, being bromantane (Fig. 1B).

The first recipients of bemilin were Soviet cosmonauts. Bemilin also was successfully employed in preparing the athletes of the USSR's national team for the 1980 Olympic Games held in Moscow. Later, throughout the 1990s, it was used as a basic medicinal agent in almost all of the corps of the Soviet and then Russian armies. Notably, its administration made it possible to increase soldiers' endurance over long marches; in the Air Forces, Missile Troops, and Army Air Defense, it enhanced work capacity and stability to hypoxia; and in the Navy, it reinforced stability to hypoxia and, where applicable, high temperatures. The latter property, in fact, had determined its wide use by the "limited contingent" of Soviet troops in Afghanistan. Bemilin enabled soldiers, including Special Forces, to effectively perform combat missions under both hypoxic and high-temperature conditions. Bemilin's effectiveness for various types of activities was shown also in its enhancement of the physical and mental capacities of rescue and other workers deployed in the wakes of the Chernobyl catastrophe (1986), the earthquakes in Armenia (1988), and the railway accidents in Bashkiria (1989) (Shabanov, 2009a). Bromantane also was employed in the Soviet and Russian armies, to shorten recovery times after strong physical exertion, though not as widely as bemilin.

After the disintegration of the USSR in 1991, the official manufacture and clinical use of bemilin was discontinued. However, owing to its wide-ranging pharmacological activity, high efficiency, and safety, its initial sports and military medicine applications have been extended widely to other branches of practical medicine. As for bromantane, its production continued after 1991, though its applications were limited, primarily, to sports medicine. Nowadays, bemilin is manufactured in Ukraine (commercial name: Anthopt) and is widely used in preparing Ukrainian national sport teams for international competitions. Bromantane is manufactured in Russia (commercial name: Ladasten); since 1997, anti-doping regulations have prohibited its use in sports, though it has recently been utilized in the treatment of patients with asthenic and restless-
asthenic frustration (Akilov et al., 2007).

**DEFINITION AND CLASSIFICATION OF ACTOPROTECTORS**

Actoprotectors are preparations that enhance body stability against physical loads without increasing oxygen consumption or heat production. Actoprotectors comprehend metabolic drugs of a non-consumptive class of action, which to greater or lesser extents can possess antihypoxic activity. They differ from antihypoxants, however, in that they primarily (directly) stimulate protein synthesis and increase working capacity. Moreover, under hypoxic conditions, they exert an antihypoxic influence that can become stronger as a result of mitochondrion-decreased ability to oxidize substrates under higher physical loads, but they do not function in this way in other pathologies.

The principal difference between actoprotectors and psychostimulants (e.g., caffeine, dextrose, phenamine, methylphenidate, modafinil, adrafinil, armodafinil) is that actoprotectors are agents of non-exhaustive action. With actoprotectors, there is no increase in oxygen consumption or heat production; and, unlike nootropic agents – actoprotectors increase not only mental (intellectual) but also, and primarily, physical work capacity.

The distinction between actoprotectors and adaptogens is not straightforward. Their respective characteristics show many similarities and even identities. It was contended that the separation of actoprotectors as a new class of pharmacological compound was not justified theoretically, that is, that this classification was the result of the practical requirements of military medicine. Agents in the actoprotector class can reasonably be referred to as synthetic adaptogens, and their strong actoprotective effect can be regarded as a component of their adaptogenic action.

Our own opinion is that actoprotectors, most logically, should be regarded as synthetic adaptogens having a strong positive influence on physical work capacity. This means that for pharmacological classification convenience, some synthetic adaptogens that significantly enhance physical performance can be termed “actoprotectors” but that other synthetic adaptogens cannot. For example, benzimidazole derivatives dibazol (bendazol), levamisole and afobazol (Fig. 2), in the literature, have been considered to be adaptogens. Dibazol’s adaptogenic action was first realized in the context of immune-mechanism-enabled adaptation to difficult environmental conditions (Rusin, 1962a, 1962b, 1963a, 1963b, 1963c, 1967; Ratnikov and Nesterenko, 1984; Novikov and Botnovskii, 1985; Udintsev et al., 1991; Sidirova and Kikova, 2000); levamisole’s adaptogenic activity also is connected primarily with adaptive immune system changes (Vaskanian et al., 1986; Alvarez-Pellitero et al., 2006; Chen et al., 2008; Fabrizi et al., 2010); afobazol has neuroprotective properties established, in vitro, by survival of HT-22 neurons in a model of oxidative stress and glutamate toxicity (Zenina et al., 2005), and its adaptogenic action is realized through central nervous system adaptation (Uyanaev and Fisenko, 2006; Litvintsev et al., 2007; Bogdan et al., 2011). As reflects their adaptogenic properties, benzimidazole derivatives are related to bemil, but their influence on physical work capacity is either absent or minimal. In light of this fact, they cannot be referenced as actoprotectors. A concise definition of actoprotectors, in our opinion, is as follows: “synthetic adaptogens with a significant capacity to increase physical performance”.

Further characteristics of actoprotector action provided are as follows:

1. These agents have minimal pharmacological activity, which explains why the mechanism of their action is difficult to correlate with their influence on some concrete types of pharmacological receptors;
2. The efficacy of these drugs for rapid recovery is maximal only when they are administered immediately after exposure to extreme conditions;
3. The strongest effect of actoprotectors is observed in persons with low or middle resistance to extreme conditions, and they are almost absent in persons with high resistance;
4. The phenomena of resistance to extreme conditions are determined not by one concrete biochemical process, but by a complex of them, primarily the speed of their changes in the body as a response to extreme conditions;
5. The most optimal agents for resistance enhancement are agents that decrease entropy by transferring to a lower functional level the “fastest” parameters of reactivity: oxygen consumption, body temperature, heart rate;
6. Actoprotectors’ principal efficacy is independent of extreme conditions (physical load, stress, hypoxia, ischemia, hypoperfusion, gravitational overload etc.); which fact suggests their influence on the basic mechanisms of resistance;
7. Administration of actoprotectors (for example bemil) can modify specific effects of many pathogenic chemotherapeutic and somatic direction’s drugs. This fact is a strong theoretical basis for co-administration of actoprotectors and pathogenic