Acetylsalicylic acid and its complex compounds with metals: mechanisms of skin microhemodynamic changes

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Abstract. The effect of acetylsalicylic acid and its complex compounds with metals (cobalt, zinc, nickel and manganese) at a dose of 10 mg/kg for 20 days on rat skin microhemodynamics was studied. It was established that acetylsalicylic acid and tested salicylates effectively modulated the skin microcirculation indices in the experimental animals. It depended on the metal in the injected compound composition and on the duration of tested salicylates administration. This demonstrated the cumulative effect of metal salicylates.

1. Introduction

Acetylsalicylic acid (aspirin, ASA) and its complex compounds with metals are used in the treatment and prevention of coronary heart disease, chronic heart failure, hypertension and other diseases of the cardiovascular system (CVS). However, ASA, along with the proven positive therapeutic effects, is a leader among all nonsteroidal anti-inflammatory drugs, not only in terms of the volume of use, but also in the total number of side effects. Therefore, it is promising to create complex compounds of ASA in order to enhance the physiological effects characteristic of the parent molecule, the appearance of new useful biological properties, to reduce side effects and resistance to aspirin therapy, and, consequently, to increase the therapeutic potential of the initial compound to obtain effective new-generation drugs.

In our studies, dose-dependent cardiotropic effects of salicylates of cobalt (ASCo²⁺), zinc (ASZn²⁺), nickel (ASNi²⁺) and manganese (ASMn²⁺) on the rat central and peripheral hemodynamics indices at doses of 5, 10 and 20 mg/kg were shown. These effects differ from the effects of ASA [1, 2]. Given that its cumulative effect is observed with daily use of low doses of ASA [3], in clinical practice it showed the use of ASA in the therapeutic dose for a long time (14 days or more).

In this regard, it was relevant to study skin microcirculation (MC) indices in the rats exposed to ASA and salicylates of cobalt, zinc, nickel and manganese with repeated administration at a dose of 10 mg/kg and to identify the dependence effects of these compounds on the duration of their administration. This was the purpose of our research.

2. Material and methods

Experimental studies were conducted on 60 male Wistar rats weighing 180-250 g, which were quarantined at least 14 days. The animals were kept in the standard vivarium conditions at a temperature of 18-22° C on Rehofix MK 2000 corncob bedding, with a natural 12-hour light-dark
cycle, free access to water (the State Standard 33215-2014 “The Guidelines for the Maintenance and Care of Laboratory Animals. Rules for Equipment of Premises and Organization of Procedures”) and complete granulated feed according to the State Standard R-50258-92. The study was carried out in accordance with rules of the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

After preliminary selection, the animals were divided into 6 groups of 10 rats each. The first group (control) included animals receiving intraperitoneal injections of saline solution (NaCl, 0.9 %). Animals of the 2nd – 6th groups were given intraperitoneal injections of 0.2 ml ASA, ASCO\(^{2+}\), ASZn\(^{2+}\), ASNi\(^{2+}\) and ASMn\(^{2+}\)at a dose of 10 mg/kg, respectively. The substances to be tested were synthesized at the Department of General and Inorganic Chemistry of the Faculty of Biology and Chemistry (Taurida Academy, V. I. Vernadsky Crimean Federal University). The purity grade was not less than 98.0%. Intraperitoneal injections of ASA and its derivatives were carried out daily for 20 days at the same time of the day (from 8.00 to 11.00 hours).

Using the method of laser Doppler flowmetry (LDF) on the device “Lazma-MC” (RPE “Lazma”, Russia), the skin MC indices in the rats were registered on the 1st, 5th, 10th, 15th and 20th day for 20 minutes after the introduction of the compounds. The studies were conducted in accordance with the existing recommendations [4, 5].

In the course of the study, we evaluated non-oscillatory (Blood perfusion (BP; perf. unit); mean square deviation (flux, MSD, \(\sigma\); perf.unit); coefficient of variation (CV; %)) and oscillatory MC indices (normalized amplitudes of endothelial (Ae), myogenic (Am), neurogenic (An), respiratory (Ar), and cardiac (Ac) rhythms), the values of which were computed using LDF 2.20.0.507WL software for processing LDF-grams [4, 5]. Neurogenic (NT) and myogenic (MT) tones, bypass grafting (BG) and nutritive blood flow (BFnutr.) were calculated according to [4, 5]. Since the distribution of the variable values was different from the normal, we applied non-parametric statistical methods. Statistical significance of the differences between the control and experimental groups were determined using the Mann–Whitney U test.

3. Results and discussion

After administration of ASA into the animals for 1 – 15 days of observation, there was a statistically significant increase in the amplitudes of endothelial Ae oscillations, most pronounced by 82.18 % (\(p<0.05\)) after 10-fold administration. However, after 20-fold administration of ASA, the Ae values approached those in the control group, as evidenced by the absence of statistically significant differences (see Figure 1-a).

Similar to the action of ASA, but expressed to a greater extent, the introduction of ASCO\(^{2+}\) led to an increase in Ae after 1 – 15-fold administration, but after 20-fold administration of this compound, there was a statistically significant decrease in Ae by 38.48% (\(p<0.05\)) and 39.71% (\(p<0.01\)), both relative to the values of this indicator in the control group and in the animals receiving ASA injections, respectively.

Similar Ae dynamics were observed after administration of ASNi\(^{2+}\) and ASZn\(^{2+}\) into the animals (see Fig. 1-a). However, there were certain differences: a decrease in the values of this indicator was registered after 15-fold administration of ASZn\(^{2+}\) by 42.57 % (\(p<0.05\)) relative to the animals of the 2nd group, and after 20-fold administration of this compound by 28.75 % (\(p<0.05\)) and 43.54 % (\(p<0.001\)) both relative to the values of this indicator in the control group and in the animals treated with ASA, respectively (see Figure 1 – a).
Figure 1 (part 1). Dynamics of the amplitudes of endothelial (a), myogenic (b) neurogenic (c), respiratory (d), pulse (e) rhythms and microcirculation index (f) in animals after 20-fold administration of acetylsalicylic acid (ASA) and salicylates of cobalt (ASCo\(^{2+}\)), zinc (ASZn\(^{2+}\)), nickel (ASNi\(^{2+}\)) and manganese (ASMn\(^{2+}\)) compared to those in the control animals (taken as 100 %).

Notes:

* – significance level of differences vs. the control group of animals (Mann–Whitney U test);
# – significance level of differences vs. ASA group of animals (Mann–Whitney U test).
Figure 1 (part 2). Dynamics of the amplitudes of endothelial (a), myogenic (b) neurogenic (c), respiratory (d), pulse (e) rhythms and microcirculation index (f) in animals after 20-fold administration of acetylsalicylic acid (ASA) and salicylates of cobalt (ASCo$^{2+}$), zinc (ASZn$^{2+}$), nickel (ASNi$^{2+}$) and manganese (ASMn$^{2+}$) compared to those in the control animals (taken as 100%).

Notes:

* – significance level of differences vs. the control group of animals (Mann-Whitney U test);
# – significance level of differences vs. ASA group of animals (Mann-Whitney U test).

A decrease in Ae at an even earlier time was observed after the administration of ASMn$^{2+}$ into the animals. Thus, after an increase in Ae by 72.53 % ($p<0.05$) and 26.13% ($p<0.001$) relative to the values in groups 1 and 2, respectively, on the 1st day of observation, starting from the 5th day of administration of this substance, a decrease in the amplitude of the rhythm of endothelial genesis.
relative to the values of this indicator was registered in the animals treated with ASA. The most pronounced decrease in Ae was observed in the animals of this group after 20-fold administration of the compound by 41.64 % (p<0.05) and 42.81% (p≤0.001) relative to the values in groups 1 and 2, respectively (see Figure 1-a).

Slow fluctuations of the endothelial rhythm characterize the state of nutritive blood flow and reflect the effect of humoral and metabolic factors on the MC channel, synchronized with the periodic release of nitric oxide (NO) by the vascular endothelium, which plays a vasodilating role and provides physiological regulation of vascular smooth muscle tone [6]. It is likely that the observed increase in the amplitude of endothelial rhythms recorded when the animals were administered ASA (1-15 days), ASCo\(^{2+}\) (1 – 15 days), ASNi\(^{2+}\) (1 – 15 days), ASZn\(^{2+}\) (1-10 days), ASMn\(^{2+}\) (1 day) indicates an increase in the basal level of NO secretion, which contributes to vasodilation of microvessels. However, longer administration of the tested salicylates into the animals led to a decrease in the amplitudes of endothelial rhythms, and, consequently, to a decrease in NO secretion, which is often observed in the development of pathological processes [7].

The analysis of myogenic rhythms amplitudes (Am) showed that under the action of ASA, there was an increase in Am at all follow-up periods, especially pronounced after 5-fold administration by 79.68 % (p < 0.05) relative to the values in the control group of rats (Fig. 1-b).

Similarly to the action of ASA, the introduction of ASCo\(^{2+}\) led to an increase in the myogenic rhythms amplitudes, expressed to a greater extent after a single administration by 64.07% (p<0.001) and 36.32% (p<0.001), compared to the same indicator in the control group and in the animals treated with ASA, respectively. However, after 20-fold administration of ASCo\(^{2+}\), on the contrary, there was a statistically significant decrease in Am values by 20.46 % (p≤0.001) and 40.86% (p≤0.001) compared to the values of the same index in the control group and in the animals receiving ASA injections, respectively (see Figure 1-b).

Similar dynamics of Am was observed when ASNi\(^{2+}\) and ASZn\(^{2+}\) were administered into the animals (see Figure 1-b), but after a single administration of ACNi\(^{2+}\), no statistically significant differences were registered compared to the control. In addition, a decrease in the values of this indicator was registered after 15-fold administration of ASZn\(^{2+}\) by 16.01 % (p<0.05) compared to the animals of group 2, and after 20-fold administration of this compound by 29.20 % (p<0.05) and 47.36% (p<0.001) both compared to the same index in the control group and in the animals treated with ASA, respectively (see Fig. 1-b).

After the administration of ASMn\(^{2+}\) into the animals, a statistically significant decrease in Am was registered throughout the entire duration of the experiment, both relative to same index in the control group and in the animals treated with ASA, respectively. It should be noted that the most pronounced decrease in Am was registered after 15-fold administration by 41.03 % (p<0.05) and 51.78% (p<0.001), relative to the same index in the animals of groups 1 and 2, respectively (see Fig. 1-b).

It is known that myogenic high-amplitude oscillations are caused by the periodic activity of smooth muscle fibers of arterioles, leading to the change in the diameter of their lumen (vasomotion). They are recorded not only at the level of sphincters, but also more proximal arterioles, which is an adaptive neurotrophic mechanism that significantly increases the number of functioning capillaries and the direction of blood flow from arterioles to the capillary bed [4].

Thus, a significant increase in Am during the administration of ASA into the animals throughout the entire study period, as well as ASCo\(^{2+}\) (1 – 15 days), ASNi\(^{2+}\) (5-15 days) and ASZn\(^{2+}\) (1-10 days), indicates an increase in the activity of precapillary sphincter myocytes and precapillary metarterioles. This is accompanied by dilation of the precapillaries, an increase in the number of functioning capillaries, and, as a result, to the priority flow of blood into the nutritive bed. This is confirmed by a decrease in the myogenic tone (MT) of the precapillary sphincters during the specified observation periods in animals of these groups. However, with longer administration of ASCo\(^{2+}\) (20 days), ASNi\(^{2+}\) (20 days) and ASZn\(^{2+}\) (15-20 days), and especially ASMn\(^{2+}\), there was a decrease in Am during the entire duration of the experiment against the background of an increase in MT. These changes indicate the development of constriction of metarterioles and precapillary sphincters, which perform a
distributional function in the skin and make the maximum contribution to the formation of intravascular resistance at the microcirculatory level. The relationship of precapillary tone with capillary density [4] gives grounds to interpret the constriction of precapillary sphincters as a reaction in response to a decrease in capillary density in the skin of animals with prolonged administration of salicylates. This is also evidenced by a significant decrease in BFnutr., which is a confirmation of a decrease in blood flow to the capillary bed.

After repeated administration of ASA into the animals, there was a statistically significant increase in the amplitudes of neurogenic oscillations (An) compared to the control group. The most pronounced increase in An was registered after 5-fold administration of ASA (by 49.08 % (p<0.05)), which is confirmed by a decrease in NT of precapillary resistive microvessels by 60.00 % (p<0.05) compared to the values in the control group. After 20-fold administration of ASA, the An values approached those in the control group, as evidenced by the absence of statistically significant differences (see Figure 1-c).

Injections of ASCo^{2+} also led to an increase in An, expressed to a greater extent after 1-10-fold injections, but after 20-fold administration of this compound, there was a statistically significant decrease in An by 32.08% (p≤0.05) and 35.08 % (p≤0.001) against the background of an increase in HT, both relative to the values in the control group and relative to the group of animals treated with ASA, respectively (see Figure 1-c).

Similarly to the action of ASA and ASCo^{2+}, the action of ASNi^{2+} also resulted in an increase in An, most pronounced after 5-fold administration by 59.36 % (p<0.05) against the background of a decrease in HT by 65.00 % (p<0.05) relative to the values in the control group of animals. After 20-fold administration of ASNi^{2+}, the An values decreased by 35.02 % (p<0.05) and 37.88% (p<0.05), both relative to the values in the control group and in animals treated with ASA, respectively (see Figure 1-c).

Daily injections of ASZn^{2+} in the animals also led to an increase in An by an average of 44.80 % (p<0.05) after 1-, 5- and 10-fold administration compared to the control group. However, after 15-fold administration of this compound, a decrease in rhythm amplitudes was registered by 31.88 % (p<0.05) and 49.46 % (p<0.05), and after 20-fold administration – by 36.48 % (p<0.05) and 39.28 % (p<0.001), both compared to the same index in the control group, and in the animals treated with ASA, respectively (see Fig. 1-c).

A decrease in An at an even earlier time, starting from the 5th day of administration, was observed after the injection of ASMn^{2+} into the animals. The most pronounced decrease in An was registered after 10-fold administration of this salicylate by 23.61 % (p<0.05) against the background of an increase in HT, both compared to the values in the control group, and by 43.33 % (p<0.001) compared to those in group 2 animals (see Figure 1-c).

It is known that the changes in the amplitudes of LDF-gram oscillations in the neurogenic range are associated with sympathetic adrenergic effects on the smooth muscles of arterioles and arteriolar areas of arteriovenular anastomoses and reflect a decrease in peripheral resistance in these areas of the microcircus [4]. Therefore, a marked increase in the amplitudes of flaxmotions in the neurogenic frequency range in the LDF-gram of animals in response to the introduction of ASA and salicylates Co^{2+}, Ni^{2+} and Zn^{2+} at the early stages of the experiment indicates a decrease in the control of arteriolar tone on the part of the sympathetic nervous system. This is confirmed by a decrease in the NT of precapillary resistive microvessels. On the contrary, after 15-20-fold injections of salicylates Co^{2+}, Ni^{2+} and Zn^{2+} and, starting from the 5th day of administration of ASMn^{2+}, there was an increase in sympathetic adrenergic activity, a decrease in the lability of the vascular wall, an increase in its rigidity and peripheral resistance, which significantly limits the possibility of blood filling of microvessels. These changes indicate constriction of metarterioles and precapillary sphincters.

Against the background of an increase in the amplitudes of active, tone-forming factors of MC regulation under the influence of ASA and the tested salicylates, changing in the activity and passive components of microvascular tone regulation, i.e. factors that cause fluctuations in blood flow outside the MC system, was observed. Thus, after repeated administration of ASA and all tested salicylates, an
increase in the respiratory rhythm amplitudes (Ar) was noted, especially pronounced after a single administration of ASCo\(^2\) (by 154.76% compared to the control). (see Fig. 1 – d).

An increase in the amplitude of the respiratory wave, which in the LDF-gram is caused by periodic pressure fluctuations in the venous part of the MC, indicates venous fullness, and, possibly, a violation of venous outflow [8].

After 1-10 – fold injections of ASA, ASCo\(^2\), ASZn\(^2\), as well as 5-10-fold injections of ASNi\(^2\) and ASMn\(^2\), a statistically significant increase in heart rate amplitudes (pulse wave from the arteries) was registered compared to the same index in the control group of rats, which is directly proportional to the change in blood flow in the MC system due to pulse blood filling (see Figure 1 – e). After 15-20-fold administration of tested salicylates, the Ac values approached those in both the control and the group of rats with ASA, as evidenced by the absence of statistically significant differences (see Figure 1-e).

The regulation in the MC system is due to the close interaction of the low-frequency and high-frequency components of the spectrum. Consequently, the increase in the respiratory amplitudes after 1-20-fold administration and pulse waves after 1-10-fold administration of ASA and its compounds with metals observed in the LDF-grams compared to the same indices in the control animal group, along with a decrease in vasomotor tone and peripheral resistance, indicates a high blood flow from the arterioles associated with vasodilation and restriction of venous outflow, which leads to tissue hyperemia in animals of these groups at the specified time. However, the increase in blood pressure and As against the background of a significant increase in vasomotor tone after 20-fold administration of ASCo\(^2\) and ASNi\(^2\), 15-20-fold administration of ASZn\(^2\) and 5-20-fold administration of ASMn\(^2\) indicates that the decrease in venous outflow with prolonged administration of salicylates occurs as a result of precapillary sphincters constriction and a decrease in capillary density in the animals skin.

The revealed changes in the regulatory mechanisms of MC in the animals as a result of the administration of ASA and the tested salicylates led to a change in the integral index of microcirculation (IM) (see Fig. 1-g), reflecting the average value of perfusion in capillaries, arterioles and venules [9]. Important factors determining changes in perfusion include the speed of movement of red blood cells, the amount of tissue hematocrit and the diameter of blood vessels, which are under the control of active mechanisms [8]. Therefore, the changes in IM under the influence of the tested compounds were of a multidirectional nature and depended on the duration of their administration. Thus, with repeated administration of ASA, an increase in the values of IM compared to the same index in the control animal group, the most pronounced (by 31.47 %; \(p<0.05\)) after a single administration (see Fig. 1-g), which was a consequence of the modulation of microcirculatory processes by active regulatory mechanisms: increased endothelial production of vasodilators, decreased activity of sympathetic efferents, and dilation of smooth muscle precapillaries. With the introduction of ASCo\(^2\), an increase in the IM values compared to the control was also noted, however, after 20-fold administration, a statistically significant decrease in the IM by 24.40% (\(p\leq0.05\)) was noted compared to the control animal group.

After the administration of ASNi\(^2\), the MI increased significantly compared to the control and amounted to 118.68 % (\(p<0.001\)) on the 15th day of observation, but after 20-fold administration, there was a statistically significant decrease in this indicator by 25.39% compared to the same index in the control animal group.

Under the action of ASZn\(^2\), a statistically significant increase IM was observed by 32.87 % (\(p<0.001\)) after a single administration and by an average of 19.84% (\(p<0.001\)) after 5-10-fold administration compared to the control animal group. However, on the following day of administration of ASZn\(^2\), there was a decrease in IM values: after 15-fold administration by 29.23% (\(p<0.05\)) compared to the animal group receiving ASA injections; after 20-fold administration – by 33.13% (\(p<0.05\)) and 29.49% (\(p<0.05\)), both compared to the same index in the control animal group and in the animal group treated with ASA, respectively. This, apparently, was the result of a pronounced decrease in NO secretion, an increase in myogenic and neurogenic tones.
The most pronounced decrease in the IM values by 27.00 % (p<0.05) and 44.08% (p<0.05) compared to the groups 1 (control) and 2 (ASA), respectively, was observed after 10-fold administration of ASMn^{2+}, but after 20-fold administration, IM increased to the level of the control group (see Figure 1-g).

Thus, in our studies it was established that under the influence of ASA and ASCo^{2+}, ASZn^{2+}, ASNi^{2+} and ASMn^{2+}, there was an effective modulation of skin MC indices in the experimental animals. It depended both on the metal in the injected compound composition and on the duration of tested salicylates administration. This demonstrated the cumulative effect of metal salicylates and is consistent with the scientific literature data [10, 11].

ASA and its compounds with cobalt, zinc and nickel for 1 – 15-fold administration causes an increase in perfusion, the diameter of the precapillaries and the number of functioning capillaries, a decrease in peripheral resistance, and, consequently, vasodilation of microvessels, an increase in blood flow to the nutritive microvascular bed against the background of a decrease in venous outflow. This may be due to the ability of these salicylates to block platelet cyclooxygenase (COX), followed by the inhibition of the synthesis of prostaglandins from arachidonic acid, which leads to inhibition of the function of thromboxane synthetase and, as a result, a decrease in the formation of the active proaggregant thromboxane A2, while the level of prostacyclin, a powerful natural vasodilator and antiaggregant, remains quite high [12], which is reflected in the development of hyperemia. However, after 15-20-fold injections of ASA derivatives with cobalt, zinc, nickel, as well as 5-20 – fold injections of ASMn^{2+}, vasoconstriction of metarterioles and precapillaries, a decrease in the lability of the vascular wall and an increase in its rigidity were registered. This leads to an increase in peripheral resistance, a decrease in the number of functioning capillaries and significantly limits the possibility of blood filling of microvessels. These changes occur against the background of increased blood filling of the venular link of the MC channel, which can serve as an anti-ischemic protective mechanism that contributes to increased blood flow to the capillaries. This type of changes in tissue microhemodynamics, apparently, is due to the fact that ASA derivatives with manganese, as well as with zinc, nickel and cobalt as a result of cumulative action after repeated administration, acetylate COX–1 in all tissues, including endothelial cells, simultaneously with a decrease in the synthesis of thromboxane A2, can inhibit the formation of prostacyclin – a natural antiplatelet and vasodilator, which leads to the development of microvascular vasoconstriction.

The obtained data confirm the cardiotropic effectiveness of new coordination compounds with divalent metals and prove that the creation of such compounds based on ASA allows not only to enhance the physiological effects characteristic of ASA, but also to obtain completely new, different from the precursor molecule. In particular, Zn^{2+} has been shown to have a vasodilating effect on blood vessels by interacting with NO-synthase [13], and Co^{2+} increases the expression of erythropoietin, vascular endothelial growth factor (VEGF), and NO-synthase genes, which leads to the improved blood oxygenation and maintenance of vascular tone. Not much is known about the role of other trace elements in the functioning of the CVS. However, it has been established that nickel plays an important role in the formation and effects of cGMP, a signaling agent that regulates various physiological processes [14].

In recent years, it has been established that complex compounds of ASA with metals can change the activity of number enzymes. For example, in the experiments of S. Korkmaz et al. (2011) in rats, it was shown that zinc aspirinate (5 days, 100 mg/kg) has a cardioprotective effect in the isoprenaline infarction model by preventing a decrease in the level of superoxide dismutase 1 (SOD 1) mRNA [10]. The latter effect is related to the structure of SOD 1, which contains a copper atom in the active center and requires zinc to stabilize the protein structure [15]. It was found that not only SOD1, but also many other enzymes have metal atoms in their structure and/or are able to bind to them: nickel (SOD, glyoxylase I, etc.) [16], manganese (SOD, catalase, arginase, etc.) [17], cobalt (carboxypeptidase, carbonic anhydrase, alcohol dehydrogenase, etc.) [18], and zinc regulates the activity of more than 300 different enzymes (oxidoreductase, lyase, hydrolase, etc.). transferases, etc.) [19]. Some of these enzymes take an important part in the functioning of the antioxidant and cardiovascular systems of the
body, among which arginase II can be noted as a promising pharmacological target in the correction of endothelial dysfunction and a number of cardiovascular diseases. The possibility of complexation of ASCs with transition metals suggests that certain salicylates biological effects may be associated with interaction with metalloenzymes [20].

4. Conclusion
1. Under the influence of repeated administration of acetylsalicylic acid and salicylates of cobalt, zinc, nickel and manganese, an effective modulation of skin microhemodynamics indices in the experimental animals occurred.
2. The modulation of skin microhemodynamics indices in the experimental animals under the influence of acetylsalicylic acid and salicylates of cobalt, zinc, nickel and manganese depends on the metal in the composition of the injected compound.
3. The modulation of the parameters of skin microhemodynamics indices in the experimental animals under the influence of acetylsalicylic acid and salicylates of cobalt, zinc, nickel and manganese depends on the duration of the tested salicylates administration.

5. References
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