REVIEW ARTICLE

SOME RECENT ADVANCES IN THE PHARMACOLOGY OF SALICYLATES

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Introduction

The naturally occurring salicylate compounds which are found in the barks, leaves and fruits of many plants and trees are very ancient remedies. The leaves of the willow, which contain the glycoside salicin, were used by Hippocrates, Celsus and Galen in the treatment of such diverse conditions as ulcers, erysipelas and prolapse of the uterus. The salicylate-bearing plants occupied a prominent place in the herbals of the Middle Ages and Renaissance.

The modern history of salicylates began in 1874 when synthetic salicylic acid became available and the discovery of its properties as an antiseptic and antipyretic soon followed. In 1876 its specific action in rheumatic fever was recognised and the analgesic action of acetylsalicylic acid was rapidly discovered. Few drugs have enjoyed such an uninterrupted popularity as salicylates. Their use has increased enormously with time, the present annual production in the U.S.A. alone being 6,000 tons, and it has been calculated on the basis of this figure that the American public must suffer at least half a billion headaches a year. A large number of salicylate compounds have been introduced into medicine but only sodium salicylate and acetylsalicylic acid are at present widely employed.

The published work on salicylates was reviewed in 1927 by Hanzlik[1] and in 1948 Gross and Greenberg[2] compiled a bibliography containing more than 4,000 references. An excellent review of the pharmacology of salicylates appeared in 1949[3] and the aim of the present article is to supplement this by discussing certain selected topics which have received attention in recent years.

Metabolism of Salicylates

(1) *Salicylic acid.*

The most important route for the elimination of ingested salicylates is the urine, although traces may be excreted in the sweat and fæces.[4] The important urinary metabolites of salicylic acid in man were shown by Kapp and Coburn[5] to be (*a*) unchanged salicylate, (*b*) salicyluric acid, the glycine conjugate, (*c*) glucuronide conjugates of two types, in one of which glucuronic acid is linked to the carboxyl group of salicylic acid and in the other is linked to the hydroxyl group, (*d*) gentisic acid, 2:5-dihydroxy-benzoic acid. In addition these workers isolated a more complex substance "uraminosalicylic acid" which had previously been reported by Baldoni.[6]

The metabolism of salicylate in man has recently been studied by a combination of radio-active tracer techniques in conjunction with counter-current distribution and chromatography.[7] C^{14} carboxyl salicylic acid was given to 4 patients with carcinomata and a wide variation in the ratios of the various metabolites was found. The proportions were (*a*) unchanged salicylic acid, 10 to 95 per cent., (*b*) salicyluric acid, 0 to 50 per cent., (*c*) glucuronic acid conjugates, 15 to 40 per cent., (*d*) gentisic acid, 1 per cent. or less. The occurrence of both types of glucuronic acid conjugates was confirmed but no uraminosalicylic acid was detected.

The metabolism of salicylic acid has also been investigated in other species. The rabbit excretes the same metabolites as man and in addition 2:3-dihydroxybenzoic acid[8] and conjugated gentisic acid[9] have been detected. The dog[7] and rat[10] excrete only an ether-linked glucuronide and in the latter species a conjugated gentisic acid, probably gentisyl glucuronide, has recently been identified by paper chromatography. The urinary metabolites of salicylic acid in the various species are summarised in Table I.

TABLE I

METABOLITES OF SALICYLIC ACID IN THE URINE OF VARIOUS SPECIES

Species	Metabolites (figures represent percentage of ingested dose)						Reference
	Salicylic acid	Salicyluric acid	Gentisic acid	Salicylglucuronides Ether	Ester	Other substances	
Dog ..	50	10	4 to 5	25	absent		7
Rat ..	41 to 63	<1	18–34	1–3	absent	Conjugated gentisic acid probably gentisyl glucuronide	10
Rabbit ..	85 Ether-soluble acid fraction	5	4–5	5–14	3–4	(*a*) 2:3 dihydroxybenzoic acid (*b*) Conjugated gentisic acid	8, 9
Man ..	20	55	4–8	25		Uraminosalicylic acid	5
	10 to 95	0 to 50	1	15 to 40		No uraminosalicylic acid detected	7

(2) *Acetylsalicylic acid.*

The acetyl group does not seem to be removed by hydrolysis in the gut because when isolated intestinal loops of dogs are perfused with acetylsalicylic acid, the outflowing solution contains the same quantity of free salicylate as the solution introduced.[11] The urinary metabolites are almost equal in amount after the administration of equal molar quantities of sodium salicylate and acetylsalicylic acid to human subjects.[12] It has been suggested[13] that acetylsalicylic acid could be excreted in the urine as a glucuronide in which the glucuronic acid is conjugated in an ester linkage with the carboxyl group of aspirin. Hanzlik and Presho[14] reported the presence of unchanged acetylsalicylic acid in the urine of patients given the drug, but their analyses depended upon the difference

in intensity of the colour reaction with iron before and after hydrolysis of the urine. This claim has been criticised[3] because the analytical procedures employed could also cause hydrolysis of the salicyl glucuronides present.

Normal human plasma hydrolyses acetylsalicylic acid to salicylic acid fairly rapidly and the tissues of several species of animals contain a hydrolysing enzyme which appears to be very similar to liver esterase. It is generally agreed that acetylsalicylic acid is hydrolysed after absorption but conflicting results have been obtained by various workers who have attempted to demonstrate the presence of the acetylsalicylate ion in blood. Smith, Gleason, Stoll and Orgorzalek[12] failed to detect any acetylsalicylic acid in plasma after a single dose of 2 g. of aspirin but Lester, Lolli and Greenberg[15] reported that 30 minutes after the administration of 0·65 g. of acetylsalicylic acid 25 per cent. of the salicylate in plasma consisted of the unchanged ester. Confirmatory evidence was provided by Smith[16] who found that one hour after the administration of 0·65 g. of acetylsalicylic acid approximately 30 per cent. of salicylates in the plasma were present as the unchanged acetylated form.

The available evidence therefore indicates that acetylsalicylic acid is absorbed unchanged and though it is hydrolysed to free salicylic acid in the blood, measurable quantities of the unchanged acetylated compound are detectable in the circulating plasma. The pattern of the urinary metabolites appears to be the same for both substances although this aspect of the problem deserves further investigation.

Effect on Acid/Base Balance

The *p*H of the blood lies between the narrow limits of 7·3 and 7·5 and depends essentially on the ratio of bicarbonate ion to carbonic acid in the blood. At the normal *p*H of 7·4 the ratio $B.HCO_3$:$H.HCO_3$ is approximately 19:1. Disturbances of acid/base balance may be divided into two main categories: (*a*) respiratory conditions in which the primary alteration is concerned with the carbonic acid, i.e., CO_2 in solution: (*b*) metabolic conditions in which the primary effect is a change in the bicarbonate content relative to acids other than carbonic.

If the tendency is towards an acid reaction the process is termed an acidosis and if towards an alkaline reaction an alkalosis. Thus a respiratory alkalosis is caused by a depletion of the carbonic acid content of the blood, such as occurs in hyper-ventilation due to stimulation of the respiratory centre. The ratio becomes more than 19:1 and the *p*H will rise if the bicarbonate content does not fall proportionally and in the same direction to compensate. If this compensation is not adequate the *p*H will rise above 7·5 and an alkalæmia or uncompensated alkalosis will delevop.

Similarly if the bicarbonate in the blood is diminished by the introduction of acid radicals, such as the keto-acids produced by abnormal fat metabolism in diabetes, the ratio will be less than 19:1 and the *p*H will fall unless the CO_2 content is also reduced to compensate. This tendency towards an acid reaction occurs in metabolic acidosis and if

the compensation is not adequate the *p*H of the blood falls below 7·3 and an uncompensated acidosis or acidæmia is produced.

One of the major problems in the pharmacology of salicylates is whether their primary effect is either to produce a respiratory alkalosis by stimulation of the respiratory centre or a metabolic acidosis by displacement of the bicarbonate ion by the salicylate ion in the blood.

Farber, Yiengst and Shock[17] and Reid, Watson and Sproull[18] have shown that in both normal people and patients with rheumatic fever receiving salicylates, the plasma bicarbonate falls and the plasma *p*H rises. This would appear to be very definite evidence that the primary effect of salicylates is to produce a respiratory alkalosis, but Reid[19] has reported that administration of bicarbonate to such subjects causes the *p*H to fall, whereas the extra bicarbonate should accentuate the alkalosis and cause the *p*H to rise. In salicylate poisoning, particularly in children, both the bicarbonate and *p*H may be distinctly decreased which is in favour of a primary metabolic acidosis, but these cases also show ketosis[3] and the keto-acids also displace bicarbonate.

The use of sodium bicarbonate is well known in the treatment of salicylate poisoning and is contra-indicated if salicylate produced a respiratory alkalosis because it would itensify the tendency towards an alkalosis. However the favourable effect of sodium bicarbonate is probably due to the increased urinary excretion of salicylate, more free salicylate being excreted as the urinary *p*H rises.[12] The primary effect of salicylate on acid/base balance is therefore one of the many problems which await final solution.

Effects on Carbohydrate Metabolism

Large doses of salicylates have been reported to prevent diabetic glycosuria in man and the drug was used in the treatment of diabetes during the latter part of the last century. Hyperglycæmia and glycosuria have been observed in cases of salicylate poisoning but hypoglycæmia has also been reported.[2] Morris and Graham[20] considered that in rheumatic children receiving salicylate therapy, the drug inhibited the utilisation of glucose by the tissues and diminished its storage in the liver. Cochran, Watson and Reid[21] reported glycosuria and a diminished glucose tolerance curve in a rheumatic fever patient receiving 5 g. of aspirin per day.

Starkenstein[22] found that salicylates prevented adrenaline glycosuria in rabbits, whereas Ozu[23] concluded that in the same species, small doses of salicylates caused increased glycogen synthesis in the liver and large doses acted directly on the liver causing glycogen breakdown and hyperglycæmia. Histo-chemical studies have shown that in acute salicylate poisoning in rabbits and rats there is a serious depletion in liver glycogen.[24] Barbour and Herrman[25] reported that aspirin caused hyperglycæmia in dogs.

In recent years the rat has been widely used in the investigation of the effects of salicylate on carbohydrate metabolism. Lutwak-Mann[26] observed that sodium salicylate caused a dramatic depletion of liver

glycogen content in intact rats accompanied by a glycosuria but the blood sugar level was unchanged. These effects were confirmed by Smith, Meade and Bornstein[27] except that glycosuria was not observed and Quilley and Smith,[10] using a sensitive paper chromatographic technique for the detection of glucose, found only insignificant traces of the sugar were excreted after the administration of sodium salicylate. In rats made mildly diabetic by partial pancreatectomy,[28] or severely diabetic with alloxan,[27] salicylate caused a marked reduction in the glycosuria. In the latter animals, salicylate also caused a rapid and striking fall in the blood sugar level, but did not produce any deposition of liver glycogen. Rats fed on high carbohydrate diet and injected with cortisone show glycosuria and hyperglycæmia and these effects were significantly reduced by sodium salicylate, which also prevented the action of cortisone in producing deposition of new glycogen in the liver of adrenalectomised rats.[29] Ingle[30] has also shown that if rats made diabetic by partial pancreatectomy are adrenalectomised and maintained on a steady intake of cortical hormone, then aspirin still produced a reduction in the glycosuria.

The main effect of salicylate appears to be in causing a "glucose demand," as shown by the reduction in blood sugar and glycosuria in the diabetic rats and the depletion in liver glycogen in intact animals. In the diabetic animal the glucose is not deposited as liver glycogen.[27] The possibility that it is converted to glucuronic acid which is used for conjugation with the salicylate is unlikely because the ability of rat liver to form a conjugated glucuronide from salicylate is negligible[26] and the rat excretes only 1 to 3 per cent. of injected salicylate as glucuronide conjugate in the urine.[10] Another possible mechanism to account for the disappearance of the glucose is the inhibition by salicylate of gluconeogenesis, i.e., the formation of glucose from non-carbohydrate sources such as amino-acids, which is mediated by adrenal corticosteroids. The antagonism of salicylate and cortisone would appear to favour this view. The animals fed on a high carbohydrate diet and injected with cortisone showed a negative nitrogen balance indicating an increased gluconeogenesis, but although salicylate reduced the glycosuria and hyperglycæmia in these animals it did not reduce the negative nitrogen balance.[29] However, in this animal preparation, the extra urinary nitrogen excretion will not quantitatively account for all the glycosuria and it has been suggested that adrenal cortical hormones also diminish tissue utilisation of glucose and it may be this effect which is being antagonised by the salicylate.

Other possible mechanisms are that salicylate may increase muscle glycogen deposition, glucose use in the tissues or conversion of glucose to fatty acids. The action of salicylate on the metabolism of isolated tissues has been studied by Lutwak-Mann[26] who found that the respiration of rat liver slices was unaffected except by very high concentrations of salicylate. Fishgold, Field and Hall[31] reported that the oxygen uptake of rat liver slices was unchanged by sodium salicylate but increased by sodium acetylsalicylate. These authors also reported that sodium salicylate in small concentrations increased the oxygen uptake of slices

of rat cerebral cortex but decreased it in high concentrations. The present writer (unpublished results) has found that salicylate in concentrations up to 0·02 M does not increase glycogen breakdown in rat liver slices. The effect of salicylate on carbohydrate metabolism in the rat is therefore to cause a glucose depletion although the actual mechanisms concerned are not yet defined and much further work needs to be done.

In other species the position is obscure and in man there appears to be the paradox that in at least some cases of diabetes, glycosuria is diminished whereas in normal or rheumatic subjects amounts of salicylate of approximately the same order have been reported to produce glycosuria and hyperglycæmia. The action of salicylate on this aspect of metabolism is still a relatively unexplored subject and merits more intensive studies.

Effects on Enzyme Systems

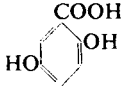
(1) *Hyaluronidase.* Hyaluronic acid is a mucopolysaccharide containing glucuronic acid and *N*-acetylglucosamine and functions as a ground substance or tissue cement in the mesenchyme. Gels formed by hyaluronic acid comprise part of the viscous barriers which in some connective tissues regulate the exchange of water and metabolites, and in other structures, such as the joints, protect internal surfaces.[32] The acid is depolymerised by an enzyme "hyaluronidase" the main effect of which is to reduce the viscosity of hyaluronic acid solutions, probably by breaking the linkages between the alternating glucuronic acid and *N*-acetylglucosamine structural units. The activity of preparations of the enzyme may be measured by this property,[33] by the decrease in turbidity of a colloidal suspension of hyaluronic acid and serum[34] or by the liberation of reducing substances from a hyaluronate substrate.[35] Hyaluronidase activity is estimated *in vivo* by means of the spreading reaction, i.e., the extent to which injected dyestuffs spread when injected into the skin.[36]

A connection between hyaluronic acid, hyaluronidase and rheumatic diseases has been suspected because the characteristic pathological lesions of these diseases are found in connective tissue. In addition the streptococcus, which has frequently been implicated in the ætiology of rheumatic fever, is one of the many micro-organisms which produce hyaluronidase. The therapeutic activity of salicylates in rheumatic conditions, particularly in rheumatic fever, has been explained on the basis that salicylates inhibit hyaluronidase, an increased activity of the enzyme being present in the disease.

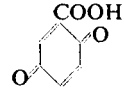
Guerra[37] claimed that Indian ink injected into the skin with hyaluronidase, spread more easily in rheumatic fever patients than in normal subjects, but this was not confirmed by other workers[38] who used hæmoglobin and Evans blue as the indicating dyestuffs. Bywaters, Holborrow and Keech[39] found that in normal subjects hyaluronidase loses its spreading effect in 24 to 48 hours, whereas in rheumatic fever patients this time is prolonged and suggested that deficient synthesis of hyaluronic acid rather than increased hyaluronidase activity was the explanation.

Salicylate has no effect on the isolated hyaluronic acid-hyaluronidase system except in relatively enormous concentrations[40] and concentrations of salicylate which are adequate for therapy are much too weak to inhibit hyaluronidase *in vitro*. Guerra[37] reported that salicylate caused a significant inhibition of the spreading power of hyaluronidase injected into the skin but although this claim has been confirmed by some workers[32,41] it has been disputed by others.[42] The discrepancy between the failure of salicylate to inhibit hyaluronidase *in vitro* and the reported activity of salicylate *in vivo* led Meyer and Ragan[43] to postulate that the metabolites of salicylate formed in the body were the true inhibitory substances. They stated that gentisic acid showed marked inhibitory properties, but Lowenthal and Gagnon[44] found that pure solutions of this substance were inactive *in vitro*. The quinone formed from gentisic acid had marked activity in similar experimental conditions but there is no evidence that this substance is a metabolite of either gentisate or salicylate.

Salicylic acid



Gentisic acid



Gentisoquinone

Some light was thrown on this confusing situation by the results of Roseman, Pearson and Dorfman.[45] These workers showed that the inhibitory activity reported for gentisic acid was due to the presence of an impurity which was probably an oxidation product. It has recently been demonstrated[46] that the appearance, in solutions of salicylate and gentisate, of inhibiting properties to hyaluronidase, may be due to production of compounds of the humic acid type. The naturally-occurring humic acids of soil and similar substances prepared from salicylic and gentisic acids were found to inhibit hyaluronidase *in vitro*. Hahn[47] has reported that polycondensation products obtained by allowing dihydroxy- and trihydroxybenzoic acids to react with formaldehyde show similar properties.

The theory that the therapeutic action of salicylate in rheumatic fever is due to the inhibitory effect of salicylate on increased hyaluronidase activity in the disease does not therefore rest on a firm basis. Firstly, there is no definite evidence that an increased activity of the enzyme is characteristic of the disease, and secondly, conflicting results have been obtained by workers who have attempted to demonstrate an "*in vivo*" inhibition of hyaluronidase by salicylate. It has been established that solutions of pure salicylic acid and gentisic acid have no inhibitory activity "*in vitro*" but certain of their oxidation products, which may be present as impurities, have marked actions in preventing the depolymerisation of hyaluronic acid by hyaluronidase.

(2) *Other Enzymes.* Salicylic acid has been reported to retard the activity of salivary ptyalin[48] and to partially inhibit the digestion of egg albumin by pepsin.[49] The salicylates also inhibit catalase activity[50] and Lutwak-Mann[26] has found that they produced some effect on xanthine

oxidase, carboxylase, indophenol oxidase and the dismutation between hexosediphosphate and pyruvate. Succindehydrogenase is markedly inhibited by salicylate.[51]

Mode of Action of Salicylates in Rheumatic Fever

There have been many theories advanced to explain the specificity of salicylates in rheumatic fever. These have been reviewed by Meade[52] who concluded that they were based primarily on current opinions of the ætiology and pathogenesis of rheumatic fever rather than on direct observations of the changes occurring in the pattern of the disease when salicylate is given.

The latest view, which has gained wide acceptance in recent years, is that the therapeutic action of salicylates in rheumatic fever is due to stimulation of the anterior pituitary and adrenal cortex leading to the production of adrenal corticosteroids which are the active agents in the therapy. This hypothesis has originated because of the concept of rheumatic fever as a disease of adaptation[53] and because of the success of adrenocorticotrophic hormone and cortisone in its treatment. There is no evidence of anterior pituitary or adrenal cortical insufficiency in rheumatic fever and adrenocorticotrophic hormone and cortisone are not being used as a replacement therapy. The theory is therefore an attempt to explain the action of an old established drug in terms of a new and successful form of therapy.

A considerable amount of evidence has been collected in support of the view that salicylates act by stimulation of the anterior pituitary and adrenal cortex, e.g., the similar clinical response to and metabolic effects of salicylate, cortisone and adrenocorticotrophic hormone in rheumatic fever[21] and similarities between the substances in certain experimental conditions in man and animals.[54] If, however, this explanation of the mode of action of salicylate is correct then the drug must act in one of the three following ways:

(1) by directly stimulating the adrenal cortex to produce adrenal corticosteroids, i.e., a direct adrenocorticotrophic hormone-like effect,
(2) by stimulating the anterior pituitary to produce adrenocorticotrophic hormone which in turn stimulates the adrenal cortex,
(3) by acting like adrenal corticosteroids or by reinforcing the action of these hormones either by increasing tissue sensitivity to them or by blocking their destruction in the tissues.

The depletion of ascorbic acid in the adrenal glands of hypophysectomised animals has been widely used as an empirical indication of adrenocorticotrophic hormone activity. Adrenocorticotrophic hormone causes a significant reduction in the adrenal ascorbic acid content in both intact and hypophysectomised rats but salicylates cause a similar result in intact rats only.[55] Therefore salicylates do not directly stimulate the adrenal in the absence of the pituitary and cannot have a direct adrenocorticotrophic hormone-like effect.

The finding that salicylates cause a depletion of adrenal ascorbic acid in intact rats has been interpreted by many workers[56] to mean that the therapeutic action of the drug is mediated through the anterior-pituitary and adrenal cortex. The specificity of this action of salicylates was investigated by the present author[57] who found that both *meta*- and *para*-hydroxybenzoic acids, neither of which have any therapeutic activity in rheumatic fever, cause a significant depletion of adrenal ascorbic acid in intact rats. The action of salicylate in causing a similar effect is therefore non-specific and bears no relation to its therapeutic activity. Other workers[58] have reported that this effect is specific to salicylates or to compounds containing the characteristic salicyl group, but have not taken into account factors such as the speed of absorption and plasma concentrations of the various substances which greatly influence the quantitative aspects of the changes in adrenal ascorbic acid content.

There remains the possibility that salicylate might act like adrenal corticosteroids, of which cortisone may be considered a typical example, or reinforce the action of these hormones in the tissues. In this case salicylates and cortisone should have identical effects on tissue metabolism. Table II shows that salicylates and cortisone not only have opposite actions on some aspects of carbohydrate metabolism but in some respects their effects are actually antagonistic.

TABLE II

EFFECTS OF CORTISONE AND SALICYLATE ON CARBOHYDRATE METABOLISM

Experimental system	Cortisone	Salicylates	Reference
1. Glycosuria of diabetic rats	Increased	Decreased	27, 28
2. Liver glycogen of adrenalectomised rats	Increased	Decreased	29
3. Rats fed on high carbohydrate diet	Glycosuria produced	Glycosuria due to cortisone decreased	29
	Hyperglycæmic curves after feeding	Hyperglycæmia due to cortisone reduced	

The currently held view that salicylates exert their therapeutic effect by stimulation of the anterior pituitary and adrenal cortex is therefore not acceptable and the mode of action of the drug is still a matter for speculation.

SALICYLIC ACID DERIVATIVES IN THE TREATMENT OF RHEUMATIC FEVER

The salicylates are extremely useful drugs in the treatment of acute rheumatic fever, but a drawback in prolonged therapy is that they produce undesirable side-effects on the gastro-intestinal tract and on the special senses. Typical symptoms which occur during salicylate administration are tinnitus, vertigo, sweating and more seriously, dyspnœa and persistent vomiting. Many attempts have been made to find allied substances with similar therapeutic effects but a greater safety margin, and a number of relatively simple derivatives of salicylic acid have recently been introduced.

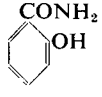
Salicylamide (I) has marked anti-rheumatic, analgesic and antipyretic properties and appears to be far better tolerated than the salicylates.[59] Its chronic toxicity in animals is less than that of aspirin[60] and it differs from salicylates in that it produces a depression of the central nervous system in laboratory animals and a decrease in the prothrombin time in man.[61] Very little conversion to free salicylic acid occurs in the body and in animals the greater part of the substance is conjugated with glucuronic acid and excreted in the urine as ether linked glucuronide.[8]

Gentisic acid (II) was introduced because of its reported inhibitory action on the enzyme hyaluronidase. Although later work, which has been discussed in the section on hyaluronidase, has shown that pure gentisic acid does not inhibit the enzyme and that increased hyaluronidase activity is probably not present in rheumatic fever, the substance appears to be a useful remedy. Its main advantage is that it is virtually non-toxic, no untoward effects having been noticed with doses up to 20 g./day. Another point of difference from salicylate is that it does not reduce the plasma alkali reserve. A limited amount of clinical information is available on the efficacy of the substance in rheumatic fever but the preliminary reports suggest that it is as active as salicylate.[62] A number of methods[63] for its estimation in blood are available and a study of the various factors which affect its plasma level has been made.[64]

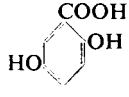
Salicylic acid is a stronger acid than its *meta*- and *para*-isomers, neither of which has any therapeutic action in rheumatic fever. This has been attributed to the close proximity of the *o*-hydroxyl and carboxyl group, the hydrogen of the hydroxyl being shared with the carboxyl group to form an additional chelate ring. Reid, Watson, Cochran and Sproull[65] argued that if such a structure was of any importance in therapeutic activity then the formation of a second chelate ring, as is possible in γ-resorcylic acid (III, IV) should enhance the activity.

The sodium salt of the acid in doses of one-tenth the usual doses of salicylate had about the same action in rheumatic fever, but undesirable side-effects seemed to be equally potentiated. However, Buttle[66] reported that its acute toxicity in mice was low and its chronic effect on the kidney tubules was less than that of salicylate. γ-Resorcylic acid differed from salicylate in producing a reduction of formalin-induced swellings in the pad of the foot in mice and also in inhibiting the formation of granulation tissue in artificial wounds on the anterior abdominal wall of mice.[67]

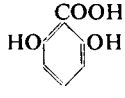
It has been suggested[68] that because a 6-hydroxyl group in the molecule of salicylic acid enhances the therapeutic activity and a 5-hydroxyl group reduces the toxicity, the introduction of both groups might provide a useful drug (V).



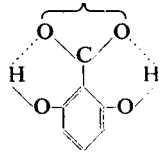
Salicylamide
(I)



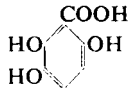
Gentisic acid
(2 : 5-dihydroxybenzoic acid)
(II)



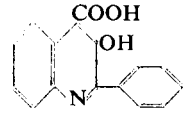
γ-Resorcylic acid
(2 : 6-dihydroxybenzoic acid)
(III)



γ-Resorcylate ion
(IV)



2 : 5 : 6-Trihydroxybenzoic acid
(V)



(3-Hydroxy-2-phenyl-cinchoninic acid) H.P.C.
(VI)

The success of cortisone and adrenocorticotrophic hormone in the treatment of rheumatic fever has stimulated a search for simpler substances with similar physiological and therapeutic actions. Certain derivatives of cinchoninic acid, which were being investigated as antidiuretics, were found to produce a stimulation of the adrenal cortex in experimental animals.[55] One of these compounds 3-hydroxy-2-phenylcinchoninic acid (VI), which showed a minimal toxicity in animal experiments was considered worthy of clinical trial.[69] It was found to be effective in a small number of cases of rheumatic fever although relapses followed the withdrawal of the drug and toxic effects such as nausea, vomiting and abdominal cramp did occur.[70] Confirmatory results were obtained by Rennie, Milne and Sommerville[71] who considered the substance was at least as good as sodium salicylate and less toxic. Hydroxyphenylcinchoninic acid has also been reported to be a potent antipyretic in animals in which artificial fevered states had been induced.[72] Rall and Wells[73] found that hydroxyphenylcinchoninic acid, but not adrenocorticotrophic hormone and cortisone, significantly reduced pyrogen-induced fever in dogs and concluded that under these conditions hydroxyphenylcinchoninic acid produces antipyresis by a mechanism other than pituitary-adrenal stimulation.

Conclusion

Recent work on the metabolism of salicylic and acetylsalicylic acids, the effects of salicylate on acid/base changes, carbohydrate metabolism and enzyme systems with special reference to hyaluronidase, has been reviewed. The theory that the therapeutic action of salicylate in rheumatic fever is due to stimulation of the anterior pituitary and adrenal cortex has been discussed critically. Some derivatives of salicylic acid which have been used in the treatment of rheumatic fever have also been reviewed.

These topics have been selected firstly, because they have received special attention within recent years and secondly, they illustrate the many unsolved problems in the pharmacology of this well-known drug.

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