Inhibitory effect of gap junction blockers on cerebral vasospasm

Laboratory investigation

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Object. The gap junction is important in the propagation of dilation/constriction signals along vessels for coordinated behavior in control of vascular tone. The authors hypothesized that gap junctions might play a role in cerebral vasospasm following subarachnoid hemorrhage (SAH). The aims of the present study were to investigate the role of gap junctions and to observe the potential therapeutic efficacy of gap junction blockers in cerebral vasospasm in vitro and in vivo.

Methods. For the in vitro investigation, the effect of heptanol on the oxyhemoglobin (HbO2)-induced contraction of isolated rabbit basilar arteries (BAs) was observed by using an isometric tension-recording method. For the in vivo experiments, the potential therapeutic efficacy of heptanol and carbenoxolone was surveyed after it was given intravenously in the rabbit double-hemorrhage model. Light microscopy was performed to assess the morphological changes in the arteries examined.

Results. For the in vitro method, heptanol significantly inhibited the sustained contraction induced both by HbO2 and K+ in the BA rings. The magnitude of the heptanol-induced relaxation was dose dependent. The inhibitory effect of heptanol on the K+-induced vasoconstriction was weaker than that on the HbO2-induced constriction. After arterial rings were pretreated for 10 minutes, heptanol significantly decreased their responses to the HbO2-induced contraction. For the in vivo method, heptanol and carbenoxolone significantly decreased the narrowing of BAs when given intravenously in the rabbit double-hemorrhage model. In both treated groups, the diameters of the arteries had not changed significantly on Day 7 compared with those of the arteries in the SAH + vehicle and the SAH-only group.

Conclusions. Heptanol and carbenoxolone significantly inhibited the experimental cerebral vasospasm both in vitro and in vivo. Blockage of gap junctions is a probable candidate for a new approach in the treatment of cerebral vasospasm. Gap junctions may play a pathophysiological role in cerebral vasospasm.

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KEY WORDS • carbenoxolone • cerebral vasospasm • endothelial gap junction • heptanol • oxyhemoglobin • rabbit

Cerebral vasospasm after SAH is a major complication following the rupture of intracranial aneurysms. Despite extensive clinical and experimental studies, the pathogenesis of cerebral vasospasm is still controversial and poorly understood. Numerous substances have been implicated in the causes of this phenomenon, but none of these investigations has determined the predominant pathophysiological mechanisms. The cause of vasospasm is presently considered to be multifactorial. Many therapeutic approaches have been suggested; however, no effective pharmacological treatment for cerebral vasospasm has been developed.

Gap junctions are one of the structures directly connecting cells. They permit the passage of ions, small molecules, and electrical current between neighboring cells due to the presence of aggregations of low-resistance transmembrane channels. The predicted intercellular diffusion through gap junctions is called gap junction intercellular communication, which may influence a wide variety of cellular activities and coordinate responses among cells and organs. Recently, experiments have provided empirical support for the functional role of gap junctions in modulating contractile responses in vascular tissues. Heptanol, a gap junction blocker, is used as a gap junction uncoupling agent to provide intercellular communication in mediating a variety of responses in multicellular preparations. Carbenoxolone, a moderately lipophilic glycyrrhetinic acid derivative used as a pharmacological gap junction blocker, has also been shown to act directly on gap junctions to block cell–cell communication, although the exact mechanism underlying this effect remains to be determined.

The present experiments were designed to confirm our hypothesis that gap junctions might play a role in cerebral vasospasm. Therefore, the effectiveness of heptanol in decreasing HbO2-induced contraction of isolated rabbit BA rings was studied in vitro, and the potential therapeutic efficacy of heptanol and carbenoxolone was observed in the rabbit double-hemorrhage model of vasospasm in vivo.
Materials and Methods

In Vitro Experiments

Sixteen New Zealand White rabbits, each weighing between 2.5 and 3.0 kg, were anesthetized with 300 mg/kg sodium pentobarbital delivered intravenously, and the animals were then killed by exsanguination from the femoral artery. The brains were removed and placed in Krebs solution composed of the following agents (in mmol/L): NaCl 120, KCl 4.5, MgSO4 1, NaHCO3 27, KH2PO4 1, CaCl2 2.5, and dextrose 10, with the addition of 95% O2 and 5% CO2 at 4°C. According to the established methods, the BAs were dissected free with the aid of magnification, and 3–4-mm-long arterial rings were prepared. A total of 64 isolated rabbit BA rings were tested. These rings were denuded of endothelium by gently rubbing the intimal surface with a stainless-steel wire, then they were suspended with rigid triangular prongs and were placed in 20-ml organ bath chambers with Krebs buffer at 37 ± 0.5°C. The chambers were continuously bubbled with 95% O2 and 5% CO2 to maintain a pH of 7.4–7.5. The Krebs solution was changed every 20 minutes. The upper and lower prongs of the tissue holder were connected to a transducer and an immovable platform, respectively. Contractions were measured isometrically with a force displacement transducer (model FT.03, Grass Instrument Co.) and results were recorded on a polygraph (model 7C, Soltel Corp.). The BA rings were initially subjected to 400 mg of basal tension over a period of 90 minutes before the experiments were performed. The rings that showed a good response to 40 mmol/L KCl were used for subsequent experiments. All agents used were added using an automatic pipette in increments of 50–200 µl. The total agent volume added for each test never exceeded 1 ml.

To confirm that the endothelium was denuded, the arterial rings were precontracted with 10−5 mol/L 5-hydroxytryptamine (also known as serotonin) and then treated with 10−3 mol/L acetylcholine. Only specimens that showed no responses to acetylcholine were used for the subsequent experiment. In the heptanol-treated group (16 rings), the arterial segments were maximally precontracted with 10−4 mol/L HbO2 or 60 mmol/L K+. After a stable response developed, a concentration response curve to the cumulative addition of heptanol (10−4–10−2 mol/L) within 10 minutes was assayed. Because complete relaxation of all the rings was achieved, the concentration response curve of the percent relaxation compared with log (mol/L) heptanol concentration was drawn. For the heptanol-pretreated group (20 rings), each ring served as its own control. Thus, after the pretreated maximal contraction with HbO2 or K+ was obtained, the rings were washed and kept stable for 1 hour, then preincubated with 2 × 10−3, 3 × 10−4, and 5 × 10−4 mol/L heptanol for 10 minutes in each concentration, and then contracted again with the same concentrations of K+ or HbO2. Graphs of the time course of the HbO2-induced response in the absence and presence of heptanol (3 × 10−4 mol/L) were drawn. In the untreated group (5 rings), the response of the BA rings to HbO2 or K+ without heptanol treatment and with pretreatment was recorded within 30 minutes. In the solvent control group (5 rings), instead of heptanol, only the solvent alcohol was used to treat and treat the arterial rings. The concentration of alcohol was the same as was used to dissolve the heptanol.

In Vivo Experiments

Thirty New Zealand White rabbits weighing between 2.5 and 3.0 kg were used in these experiments. The double-hemorrhage model of SAH used in the study has been described previously.31,32 The animals were anesthetized with 30 mg/kg sodium pentobarbital delivered intravenously, and supplemental anesthetic agents were administered during the experiment to ensure that the rabbits were as free of stress as possible. The animals were endotracheally intubated and ventilation was performed with a Bird model 8400 unit (Bird Products Corp.). The central ear artery was cannulated to obtain autologous arterial blood and to monitor the mean arterial pressure and arterial blood gas levels (i-STAT Corp.). The mean arterial pressure was monitored with a pressure transducer (model 78342A) and recorded on a chart recorder (model 78172A; both obtained from Hewlett Packard Corp.).

On Day 1 the rabbit’s neck was shaved. Using an aseptic technique, a No. 23 butterfly needle was percutaneously placed in the cisterna magna and 1 ml of cerebrospinal fluid was aspirated. Subsequently, 0.5 ml/kg nonheparinized autologous arterial blood was injected into the cisterna magna over 1 minute. The animals were then placed in a 30° head-down tilted position for 15 minutes to facilitate the settling of blood by gravity in the subarachnoid cistern. This procedure was repeated 1 day later (Day 2).

After anesthesia was induced, the rabbits were placed in a supine position, and a 5-F catheter (Terumo Corp.) was inserted selectively into the aortic arch through a femoral artery by the Seldinger method, as previously described.42 Angiograms of the BA were obtained by injection of 5 ml Omnipaque contrast medium for 2 seconds at a pressure of 50 psi. The speed of digital image acquisition was 6 frames/second. The angiograms obtained were transferred to an analytic processing system, and the diameter of the BA was measured at 5 points (at the midpoint of the BA, at 1 mm central and peripheral from the midpoint, and at 2 mm central and peripheral from the midpoint), as described previously.33 The mean diameter at these 5 points was then determined. All angiograms were obtained by one investigator, and the diameters of the BAs were measured by a colleague working in a blinded fashion. Angiograms were performed on Days 0 (baseline) and 7. We calculated the percentage of the BA diameter on Day 7 relative to its diameter on Day 0 for each rabbit.

In the SAH-only group (6 rabbits), the animals underwent SAH induction without any treatment. In the SAH + heptanol group (6 rabbits), 24 hours (Day 3) after the second injection of blood, 0.2 mmol/kg heptanol was administered intravenously and repeatedly on Days 4 and 5. Arteriograms were obtained on Days 0 and 7. In the SAH + carbenoxolone group (6 rabbits), the procedure was the same as in the SAH + heptanol group, but with 16 µmol/kg carbenoxolone administered instead of heptanol. In the SAH + vehicle of heptanol group (6 rabbits), the animals were injected with the same amount of the vehicle (alcohol) as in the SAH + heptanol group, but without the heptanol. In the SAH + vehicle of carbenoxolone group (6 rabbits), the animals were injected with the same amount of the vehicle (normal saline) as in the SAH + carbenoxolone group, but without the carbenoxolone.

The morphological changes of the arterial walls after SAH were assessed with the aid of light microscopy. In each group, 2 animals were perfusion fixed by transthoracic cannulation of the left ventricle and injection with a mixture of 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) under a pressure of 120 cm H2O. After perfusion fixation, the brain was removed and a BA segment 2 cm in length was then cut from close to the midpoint of the vessel. The segment was cut at a thickness of 0.5 µm, processed in paraffin, and stained with H & E.

Drugs Used in the Study

For these studies, serotonin, 1-heptanol, carbenoxolone, and HbO2 were obtained from Sigma Chemical Co. The serotonin was dissolved in 0.1 N HCl with 0.1% ascorbic acid. Heptanol and carbenoxolone were dissolved in alcohol and normal saline, respectively. The hemoglobin solution was prepared according to the method of Martin et al.31 The concentration of hemoglobin was measured using the cyanomethemoglobin method. Other drugs were dissolved in distilled water. The doses of agents tested were expressed as a final concentration in the bath.

Statistical Analysis

The data are expressed as the mean ± SEM. Statistical comparison was performed using the SAS computer program, and the Scheffé test was used for analysis. Significance was assumed for comparisons in which the probability value was < 0.05.

Results

In Vitro Experiments

A sustained contraction of rabbit BAs was elicited with 10−3 mol/L HbO2 and lasted > 30 minutes (Fig. 1a). The submaximal (80%) and maximal contractions were reached
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at 2 minutes and 5 minutes, respectively, after the addition of $10^{-4}$ mol/L HbO$_2$. Stronger contractions of the rings with 60 mmol/L K$^+$ were observed, which reached the maximal level within 1 minute, and lasted > 15 minutes.

In the heptanol-treated group, $10^{-4}$–$10^{-2}$ mol/L heptanol significantly inhibited the sustained contraction of BA rings induced both by $10^{-4}$ mol/L HbO$_2$ and 60 mmol/L K$^+$. The magnitude of the heptanol-induced relaxation was dose dependent (Fig. 2). With 500 μmol/L heptanol, the magnitude of the HbO$_2$-induced vasoconstriction was reduced to 60%, whereas with 1 mmol/L heptanol, it was almost completely inhibited (Fig. 1b). An inhibitory effect of heptanol on the K$^+$-induced vasoconstriction was also observed, but it was weaker than the effect on the HbO$_2$-induced vasorestriction, especially with the concentration of heptanol between $5 \times 10^{-4}$ and $5 \times 10^{-3}$ mol/L (p < 0.01; Fig. 2).

In the heptanol-pretreated group, after arterial rings were pretreated for 10 minutes, heptanol ($\geq 5 \times 10^{-4}$ mol/L) significantly decreased their responses to the HbO$_2$-induced or K$^+$-induced contraction (p < 0.01; Table 1). With the concentration of $3 \times 10^{-4}$ mol/L heptanol, the time course of HbO$_2$-induced contraction was unaltered, although the absolute magnitude of the response was decreased by nearly 40% (Fig. 3). However, with the same concentration of heptanol, the K$^+$-induced contraction was not blocked (Table 1).

After they were sufficiently washed with buffer, all arterial rings we tested had recovered to their normal responses. When the concentration was $< 5 \times 10^{-4}$ M, heptanol had no effect on the basal tension of the rings. No relaxation responses of the arterial rings to HbO$_2$ and K$^+$ in the solvent control group were observed, which excluded the effect of alcohol on HbO$_2$- and K$^+$-induced contraction at the concentrations used in this study.

In Vivo Experiments

The arterial blood pressure, PaO$_2$, and PaCO$_2$ were maintained within normal ranges in each group.

There were no significant differences in each group in terms of the normal diameters of BAs (p < 0.05; Fig. 4). The rabbit double-hemorrhage models were established successfully. In the SAH-only and SAH + vehicle groups, BA vasospasm was readily apparent on Day 7.

Heptanol and carbenoxolone significantly decreased the narrowing of the BA after SAH. In both the SAH + hep-

![Fig. 1. Graphs showing the typical pattern of 10$^{-4}$ M HbO$_2$ (OxyHb)-induced contraction (a) and a cumulative concentration of heptanol (b) in rabbit BA rings. Values on the x and y axes represent time (minutes) and tension (grams), respectively.](image1)

![Fig. 2. Graph showing the effect of heptanol on HbO$_2$- and K$^+$-induced contraction in rabbit BA rings in the heptanol-treated group. Vertical bars represent the SEM. ** p < 0.05.](image2)
is probably the principal pathogenetic factor. Many J. Neurosurg. / Volume 108 / March 2008

...channels, together with those recently it has been found that the gap junction can transfer can coordinate the cel-

Therefore, we adopted and successfully es-

...vessels showed obvious expansion on Day 7 compared with both the SAH-only and SAH + vehicle groups (p < 0.05). There was no significant difference compared with the diameters of the normal arteries on Day 0 (Fig. 4). The animals in our experiment showed no obvious abnormal symptoms associated with the adverse effects of heptanol and carbenoxolone at the dosages used. This result demonstrated that both heptanol and carbenoxolone had therapeutic efficacy in experimental cerebral vasospasm.

In necropsies performed at the end of the experiments, clotted blood was observed in the subarachnoid space and surrounding the BAs, and the subarachnoid membrane had become yellow. With light microscopy, the BAs from Day 7 rabbits in both the SAH-only and the SAH + vehicle groups had abnormalities, including condensation of chromatin in endothelial cells, corrugation of internal elastic lamina, sparse distribution of smooth-muscle cells, and so on. The vessels of the SAH + heptanol and the SAH + car-

<table>
<thead>
<tr>
<th>Dose (mol/L)</th>
<th>Heptanol</th>
<th>K⁺-Induced Contraction (g)</th>
<th>HbO₂-Induced Contraction (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 × 10⁻⁴</td>
<td>2.06 ± 0.37</td>
<td>2.25 ± 0.52</td>
<td>1.70 ± 0.33 ± 0.23</td>
</tr>
<tr>
<td>3 × 10⁻⁴</td>
<td>2.17 ± 0.33</td>
<td>2.05 ± 0.30</td>
<td>1.72 ± 0.43* 1.17 ± 0.31*</td>
</tr>
<tr>
<td>5 × 10⁻⁴</td>
<td>2.06 ± 0.23*</td>
<td>1.53 ± 0.31*</td>
<td>1.77 ± 0.38* 0.74 ± 0.30*</td>
</tr>
</tbody>
</table>

* p < 0.01.

**Discussion**

Numerous agents have been deemed responsible for vasoconstriction, including serotonin, endothelin, HbO₂, and so on. Among vasoactive agents inside and outside vessels, HbO₂ is probably the principal pathogenetic factor. Many findings suggest that the time course of the release of HbO₂ from lysed erythrocytes following SAH corresponds approximately to the development of vasospasm. Although the definite pathogenesis of cerebral vasospasm is still unclear, many possible mechanisms involved in HbO₂-induced vasoconstriction include the release of free radicals, the initiation and propagation of lipid peroxidation, the inhibition of endothelium-dependent relaxation, and the release of endothelin from the vessel wall. It was generally believed that the imbalance between the vasoconstriction signals and dilation signals results in delayed cerebral vasospasm following SAH. Cerebral vasospasm shows a typical dynamic change according to angiography. Previous reports have indicated that cerebral vasospasm is observed as early as 30 minutes (the acute phase) after SAH, and reaches a peak at 3–7 days (the chronic phase).

Among several animal models of cerebral vasospasm, the double-hemorrhage model was considered to resemble more closely the human pathological features of cerebral vasospasm. Therefore, we adopted and successfully established this model of cerebral vasospasm. In the double-hemorrhage model, it has been reported that there are a variety of morphological changes in arteries in spasm, such as endothelial cell vacuolization, disruption of the internal elastic lamina, and so on.

Gap junction channels interconnect the cytoplasms of adjacent cells to provide a pathway for the intercellular transfer of current-carrying ions and small molecules, including second messengers. The gap junction channels are relatively nonspecific and highly permeable, allowing the movement of molecules < 1000 D (such as Ca²⁺, inositol trisphosphate, and cyclic adenosine monophosphate) and electric current. Histological and molecular biological studies have indicated the presence of gap junctions among smooth-muscle cells and endothelial cells in vascular walls. Heterocellular coupling, for example endothelial cell→smooth-muscle cell coupling, can transfer signals to smooth-muscle cells to control vascular diameter, and homocellular coupling, for example smooth-muscle cell→smooth-muscle cell coupling, can coordinate the cellular behavior along the vessel wall. In a previous experiment, in which we used immunohistochemistry and confocal laser microscopy, we demonstrated that an abundance of gap junction protein (connexin) staining was found in the adventitial layer of cerebral vessels and in the pia mater surrounding them. These channels, together with those present among endothelial cells, may transfer integrated signals inside and outside the vascular lumen to smooth-muscle cells, coordinating the responses of cells and mediating the vasoconstriction and vasodilation responses in vessels. Recently it has been found that the gap junction may be involved in the pathogenesis of some vascular diseases, such as hypertension, arteriosclerosis, and cerebral ischemia.

We first developed the study of the role of gap junctions in cerebral vasospasm. The results in vitro demonstrated that heptanol, in a dose-dependent manner, significantly inhibited the sustained contraction of rabbit BA rings induced by HbO₂. In addition, the inhibitory effect of heptanol on K⁺-induced vasoconstriction was also observed in the same
range of concentrations, although the effect was weaker than that on HbO$_2$-induced constriction. The in vivo study showed that both heptanol and carbenoxolone inhibited cerebral vasospasm after SAH. Intravenous administration of these drugs after cerebral vasospasm was established had a significant therapeutic effect, as demonstrated in the SAH/Heptanol and SAH/Carbenoxolone groups.

Heptanol has been reported to reduce coupling by closing the gap junction channels by a conformational change at the connexin–membrane lipid interface, and is frequently used to investigate intercellular communication in intact smooth-muscle preparations. Generally, this is explained by an incorporation of heptanol into the lipid bilayer, leading to impairment of the transcellular gap junction channels. Many investigators use heptanol, which has been shown to inhibit gap junctions reversibly at concentrations ranging from 30 µmol/L to 2 mmol/L. Of course, it lacks specificity as a lipophilic agent at high concentrations (that is, concentrations ≥ 1–3 mmol/L). Nevertheless, there is a principle for ascertaining reasonable experimental conditions under which heptanol may be used as a “relatively selective” uncoupling agent. In our study, the concentration of heptanol is within the range of the previously reported selective concentration required for intercellular uncoupling. It has been shown that vascular tone in cerebral arteries could be attenuated by the inhibitors of gap junctions. There have been some studies investigating the mechanism of heptanol-inhibiting gap junction in animal arteries, myocardium, and so on. It is accepted that heptanol could reduce gap junction intercellular communication by dephosphorylating connexin43, and the downregulation of connexin43 may make for a delayed uncoupling, contributing to a protective effect in the cardiovascular system.

We are still not convinced, however, that the therapeutic efficacy of heptanol on cerebral vasospasm is undoubtedly due to the inhibition of gap junctions, because its nonspecific effect is so directly concerned. To exclude the possible nonselective effect of heptanol and better clarify that its effect on cerebral vasospasm is necessarily related to the action on gap junctions, we used another known gap junction blocker, carbenoxolone, in the experiment we conducted in vivo. Carbenoxolone can selectively block hemichannel current in the retina of the goldfish, and it can uncouple glial and neuronal cells in rat brainstem slices. It has also been shown to dephosphorylate connexin43 in rat liver epithelial cells. Nevertheless, the exact mechanism underlying the blocking effect on gap junctions remains to be determined. The dose of carbenoxolone used in our experiments was based on previous reports. In the present study, it is reasonable to consider that the inhibitory effect of heptanol and carbenoxolone on the experimental cere-
bral vasospasm may have contributed to their selective inhibition of gap junctions, because both blockers used in the study demonstrated the same significant results. Therefore, gap junctions may play an important role in the pathogenesis of cerebral vasospasm. Both heptanol and carbenoxolone are probably able to decrease the permeability of gap junctions or close part of the gap junction channels, resulting in reduced propagation of the spasmogenic signals through the functional network of gap junctions. The difference in the effect of heptanol on K\(^+\) and HbO\(_2\)-induced contraction may contribute to these agents' different underlying mechanisms.

Cerebral arteries generally have 4 concentric smooth-muscle cell layers across the media. The distance may limit the effective diffusion radius of neuronal- and endothelial-derived substances in the vascular wall.\(^3\) There is a certain mechanism (the gap junction) to ensure a syncytial smooth-muscle response both across and along the vessel wall. An increase in intercellular coupling could lead to greater impulse propagation among a larger number of coupled smooth-muscle cells, thus leading to exaggerated contractile responses.\(^29\) According to the experimental results and other evidence, we deduce that during the development of cerebral vasospasm, the vasospastic signals could be transmitted and synchronously regulated through gap junction channels. Gap junctions might at least facilitate some signal transmission, such as vasoactive signals, contractile signals, and so on, from endothelial to smooth-muscle cells (via myoendothelial gap junctions) or among smooth-muscle cells (via homocellular gap junctions). After SAH, gap junction channels might have a pathological change in their state, resulting in the breakdown of the balance of cerebral vasomotion. Subsequently, the change could make ion current, electric current, and second messengers triggered by the spasmogenic substance (such as HbO\(_2\)) propagate more extensively and quickly from the ruptured vessel wall to a wider area. Changing the function of gap junction channels would influence the extension and duration of cerebral vasospasm. In other words, attenuating the function of gap junctions somewhat would relieve cerebral vasospasm after SAH.

This primary research extends a new approach to the study of cerebral vasospasm. However, much work needs to be done for further investigation, such as studies of the changes in gap junction structure and function after SAH and the toxicological effects of gap junction inhibitors.

**Conclusions**

Gap junction blockers significantly inhibit experimental cerebral vasospasm in vitro and in vivo. The gap junction may play a pathophysiological role in cerebral vasospasm. Blocking of gap junctions is a possible new approach for the treatment of cerebral vasospasm.

**Acknowledgments**

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**References**


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**Fig. 5.** Photomicrographs showing representative histological structural changes of the BA on Day 7. There was no vasospasm in the normal BA group (A). Morphological vasospasm was observed in the BA rings in the SAH-only (B) and SAH + vehicle (E and F) groups. In contrast, morphological changes of vascular structure in the SAH + heptanol (C) and SAH + carbenoxolone (D) groups were significantly less than in the SAH-only and SAH + vehicle groups. The group represented in each panel is as follows: A, normal BA; B, SAH only; C, SAH + heptanol; D, SAH + carbenoxolone; E, SAH + vehicle of heptanol (alcohol); and F, SAH + vehicle of carbenoxolone (saline). H & E, original magnifications as given in the panels.
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