Naunyn-Schmiedeberg's Archives of Pharmacology (2021) 394:1879–1891
https://doi.org/10.1007/s00210-021-02092-4

ORIGINAL ARTICLE

Non-selective COX inhibitors impair memory formation and short-term but not long-term synaptic plasticity

Soomaayeh Heysieattalab[1] · Jafar Doostmohammadi[2] · Mahgol Darvishmolla[2] · Negin Saeedi[2] · Narges Hosseinmardi[2,3] · Masoumeh Gholami[4,5] · Mahyar Janahmadi[2,3] · Samira Choopani[6]

Received: 5 January 2021 / Accepted: 12 April 2021 / Published online: 3 May 2021

Abstract

Cyclooxygenase (COX) plays a critical role in synaptic plasticity. Therefore, long-term administration of acetylsalicylic acid (ASA) and its main metabolite, salicylate, as a COX inhibitor may impair synaptic plasticity and subsequently memory formation. Although different studies have tried to explain the effects of ASA and sodium salicylate (SS) on learning and memory, the results are contradictory and the mechanisms are not exactly known. The present study was designed to investigate the effects of long-term low-dose (equivalent to prophylactic dose) and short-term high-dose (equivalent to analgesic dose) administration of ASA and SS respectively, on spatial learning and memory and hippocampal synaptic plasticity. Animals were treated with a low dose of ASA (2 mg/ml solvated in drinking water, 6 weeks) or a high dose of SS, a metabolite of ASA, (300 mg/kg, 3 days, twice-daily, i.p). Spatial memory and synaptic plasticity were assessed by water maze performance and in vivo field potential recording from CA1, respectively. Animals treated with ASA but not SS showed a significant increase in escape latency and distance moved. Furthermore, in the probe test, animals treated with both drugs spent less time in the target quadrant zone. The paired-pulse ratio (PPR) at 20-ms inter-pulse intervals (IPI) as an index of short-term plasticity in both treated groups was significantly higher than of the control group. Interestingly, none of the administered drugs affected long-term potentiation (LTP). These data suggested that long-term inhibition of COX disrupted memory acquisition and retrieval. Interestingly, cognitive impairments happened along with short-term but not long-term synaptic plasticity disturbance.

Keywords Cyclooxygenase · Acetylsalicylic acid · Sodium salicylate · Synaptic plasticity · Learning and memory

Introduction

Non-steroidal anti-inflammatory drugs (COX inhibitors), especially acetylsalicylic acid (ASA), are widely used for several medical purposes including pain relief (Lipton et al. 2005), prevention of ischemic stroke, and reducing the risk of cardiovascular events (Sztriha et al. 2005). The metabolite of ASA is salicylate (Gilroy 2005), which inhibits platelet function (Roth and Majerus 1975; Roth et al. 1975). Due to its anti-platelet activity, it is used for treating 85% of patients after myocardial infarction. Also, low-dose of ASA was used as primary prevention of cardiovascular problems in individuals with no cardiovascular disease (Roth and Majerus 1975; Sairanen et al. 2011).

Although ASA is traditionally among the most widely used drugs in cardiovascular disease prevention and pain relief, it has general effects in the brain such as reducing oxidative stress and protecting against oxidative damage.

✉ Narges Hosseinmardi
nargeshosseinmardi@gmail.com; nhosseinmardi@sbmu.ac.ir

[1] Division of Cognitive Neuroscience, University of Tabriz, Tabriz, Iran

[2] Department of Physiology, Medical School, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4] Department of Physiology, School of Paramedical Sciences, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

[5] Neuroscience Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

[6] Department of Physiology and Pharmacology, Pasteur Institute of Iran (IPI), Tehran, Iran

Early evidence suggests that there are beneficial effects of aspirin in preclinical and clinical studies on mood disorders and schizophrenia, and epidemiological data suggests that high-dose aspirin is associated with a reduced risk of Alzheimer's disease (AD). Aspirin, one of the oldest agents in medicine, may be a potential new therapy for a range of neuropsychiatric disorders including depression, schizophrenia, bipolar disorder, and AD (Berk et al. 2013).

However, ASA directly and irreversibly inhibits cyclooxygenase-1 (COX-1) and modifies the enzymatic activity of COX-2 (Amann and Peskar 2002). Cyclooxygenase is an enzyme that mediates the conversion of the first stage of arachidonic acid (AA) to prostaglandin E2 (PGE2) (Vane and Botting 1992; Simmons et al. 2004; Park et al. 2006). COX oxygenating arachidonic acid forms PGG2 which in turn reduced by the same enzyme to PGH2. mPGES (microsomal prostaglandin E synthase-1) converts PGH2 to PGE2 (Smith et al. 2000; Park et al. 2006) which is a retrograde messenger, activates presynaptic PGE2 subtype 2 (EP2) receptors, modulating synaptic transmission, and is necessary for synaptic plasticity and memory acquisition (Sang et al. 2005; Yang et al. 2008). There are at least two COX isoforms, COX-1 and COX-2. In this regard, COX inhibitors differ in their ability to inhibit these isoforms (Simmons et al. 2004). Most tissues express COX-1 which is involved in diverse physiological functions (Mohammed et al. 2004), while COX-2 is expressed in both physiological and pathological conditions in the central nervous system (CNS) abundantly in the hippocampus and cortex (Yamagata et al. 1993; Mohammed et al. 2004). It has been speculated that N-methyl D-aspartate (NMDA) receptor–dependent synaptic activity regulates the expression of COX-2. Additionally, high-frequency stimulation (HFS) which is associated with long-term potentiation (LTP) induction is related to its expression (Amann and Peskar 2002; Yang and Chen 2008; Yang et al. 2008).

In addition to COX modulation, salicylate affects neuronal function through interaction with specific membrane channels/receptors, such as voltage-dependent sodium, potassium, and calcium channels, as well as GABA and glutamate receptor–mediated responses (Liu and Li 2004; Liu and Li 2004; Liu et al. 2005).

It has been shown that sodium salicylate (SS) significantly reduced GABAergic inhibition, leading to an increased neuronal excitation in the hippocampal CA1 area (Gong et al. 2008; Gholami et al. 2015). As hippocampus acts as a waypoint in receiving, processing, and transmitting information to different areas of memory storage and has high plastic potential, it has been suggested that LTP-like synaptic changes occur in this structure during the process of learning and memory formation (Yang et al. 2008; Zugaib and Leão 2018). Considering the different effects of salicylate in the hippocampus, which is a key structure for many complex brain functions such as learning and memory (Hosseinmardi et al. 2011), investigating its effect on hippocampal functions is interesting. There are different studies tried to show the involvement of COXs in hippocampal functions. For example, it has been reported that intra-hippocampal injection of COX-2 inhibitors reduces memory consolidation (Rall et al. 2003). On the other hand, expression of COX-2 is increased in the cortex and hippocampus of patients affected by senile memory abnormalities (Yermakova and O'Banion, 2001). Jonker et al. showed that ASA improves short-term memory in the healthy elderly (Jonker et al. 2003). However, there are few studies available on the protective effects of short-term use of NSAIDs on memory impairment (Rao et al. 2002). Furthermore, there are controversial findings with regard to the effects of COX inhibition on the learning process. For instance, Bruce Jones et al. (1994) found that COX inhibition has reinforcing effects on learning and memory (Bruce-Jones et al. 1994), while Holscher (1995) reported impairing effects of COX inhibition (Hölscher, 1995) that indicate the role of COX in learning and memory processes is more complex than what has been understood so far.

Considering the increasing rate of ASA consumption which inhibits COX and its consequent effects on learning and memory, the present study was designed for elucidating whether chronic low-dose consumption of ASA and also short-term treatment with a high dose of SS may affect synaptic plasticity in Schafer collateral (SC)–CA1 synapses and also memory capacity.

Materials and methods

Animals

Adult male Wistar rats with an age of 4–5 months and weight of 250–300 g were used in this study. Three to four animals were housed per cage and they had free access to food and water. The temperature of the room was controlled (22 ± 2 °C) with a 12-h light/dark cycle (lights on at 07:00 am). All of the experiments were performed during the light cycle between 10:00 am to 14:00 pm. All efforts were made to reduce the number of animals used and their suffering.

All experimental procedures were conducted following the policy of the Iranian Convention for the Protection of Vertebrate Animals Used for Experimental Purposes. The protocol was approved by the Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (February

9th, 2012; Approval number: 240, IR. Beheshti University SBMU.RECIEC 0.1390.11).

Drug administration

To assess the effect of COX inhibition on spatial learning and memory as well as synaptic plasticity, the rats were treated with SS and ASA. SS (Sigma, St. Louis, MO, USA) was dissolved in saline and administered sub-chronically with a high dose (300 mg/kg, twice-daily, i.p.) resembling the 1000-mg analgesic dose for humans (Pernia-Andrade et al. 2004) for 3 days in a row before the morris water maze (MWM) test. In other group, rats received either tap water (control) or ASA (2 mg/ml) solvated in potable water for 6 weeks. Since rats normally take 20–40 ml of water daily (depending on room temperature), it is calculable that each animal receives ASA nearly 40–80 mg/day; an amount like that utilized in humans, 75 mg, as a prophylactic agent against heart attack (Smith et al. 2002). These two different treatment schedules for SS and ASA administration were used to evaluate the effects of both short-term high-dose (analgesic dose) and long-term low-dose (prophylactic dose) treatments with the aforementioned drugs on learning, memory, and synaptic plasticity. In a pilot study, the daily water consumption was monitored in various experimental groups, especially animals drinking tap water alone and those drinking tap water containing ASA. Statistical analyses revealed that there was no statistically remarkable difference between groups (data are not shown). The protocol of the experiment is presented in Fig. 1.

Thus, the following experimental groups were evaluated in the present study:

1) Animals were treated with SS intra-peritoneally for three consecutive days before the MWM test ($n=9$).
2) Animals received saline (vehicle of SS) for three consecutive days before the MWM test ($n=7$).
3) Animals were treated with ASA in drinking water for 6 weeks ($n=7$).
4) Animals drank tap water without ASA for 6 weeks ($n=8$).

Various animals were utilized for behavioral and electrophysiological studies. Thus, electrophysiological study was performed on separated animals from behavioral assessment.

Experimental procedures

Behavioral study

All animals underwent the MWM test. The water maze apparatus consists of a large circular pool (155-cm diameter and 60-cm height) filled to a depth of 35 cm with water (22 ± 1 °C). This black-painted pool was located in a room entailing various prominent visual cues. Total pool imaginarily was divided into four equal quadrants, Northeast (NE), northwest (NW), southeast (SE), and southwest (SW). In the center of the eastern quadrant (target quadrant), a hidden platform (10 cm in diameter) made of Plexiglass was placed 2 cm under the water surface. The rats' swim path was recorded (Ethovision software XT7, Netherland) by a video-computer tracking system (CCD camera, Panasonic Inc, Japan) for later analysis. Large posters on the wall of the room were used as visual cues.

Acquisition phase Twenty-four hours prior to beginning training, rats were given a 60s swim in the tank without a platform for adjusting to the environment. After either SS or ASA treatment, training of animals was started and continued for 3 consecutive days (each day included one block of 4 trials). Placing the animal in one of the four quadrants was the beginning point for each trial (Smith et al. 2002; Choi et al. 2006). Animals were allowed to swim in the pool for 90 s to find the hidden platform that was kept in the middle of one of the four quadrants. If an animal did not find the platform within this period, it was manually guided to the

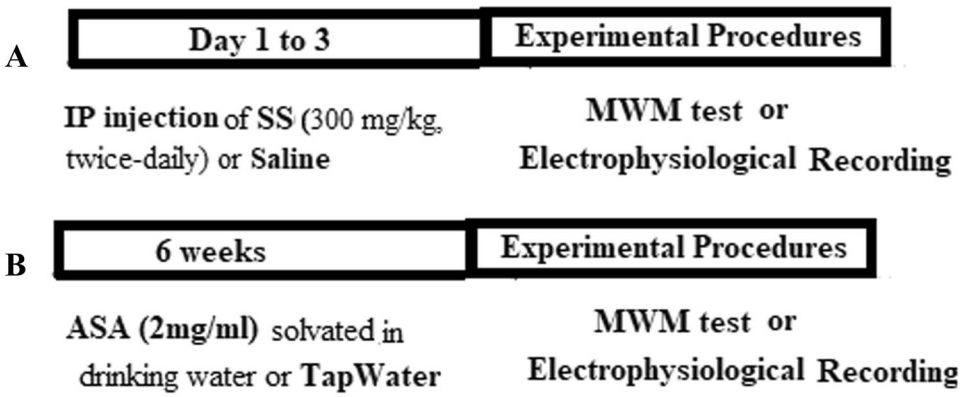

Fig. 1 Experimental protocol of the study

platform by the investigator and allowed to rest for 20 s. The rats rested 5 min between the two consecutive trials and all trials were conducted at about the same time in the morning. Several parameters including escape latency (time to find the platform), traveled distance (path length to reach the platform), and swimming speed were recorded in each trial to evaluate spatial learning ability. Swimming speed was used to assess the motor activity of the rats.

Probe test Twenty-four hours after the completion of training, the platform was removed and the rat was released into the quadrant diagonally opposite to that which previously contained the platform. During the probe trial, the rat was allowed to search for 60 s, without the platform. Duration in the target quadrant was used to assess how the rats remember the location of the platform (i.e., retention of memory).

Visible platform task Thirty minutes after the probe trial, the platform was elevated above the water surface and covered by bright color aluminum foil, and placed in a different zone (north quadrant) to test the visual acuity of the rats and their motivation to escape. The rats were allowed to swim and find the visible platform within 60 s to test their visual ability.

Electrophysiological study

For field potential recording, animals got an i.p. injection of urethane to induce anesthesia (1.5 g/kg, Sigma, USA). Then, bipolar stainless steel recording and stimulating electrodes (0.125-mm diameter, Advent, UK) were implanted into the stratum radiatum of the hippocampal CA1 area (2.8 mm posterior to the Bregma, 1.8 mm lateral to the midline) and into the Schaffer collateral (3 mm posterior to the Bregma, 3.1 mm lateral to the midline), respectively, via holes drilled through the skull (Paxinos and Watson 2006). To minimize trauma to brain tissue, the electrodes were lowered very slowly (0.2 mm/min) from the cortex to the hippocampus. The electrode insertion depth was determined by optimizing the evoked response. Recording signals were amplified by an amplifier (DAM 80, WPI, Sarasota FL, USA), displayed on an oscilloscope, and saved at 10-kHz sampling rate on a personal computer hard disk for the offline analysis.

Electrical stimulation consisted of constant current rectangular pulses (200 μs, 0.1 Hz, 100–1100 μA) and delivered by an isolator (A365R, WPI, Sarasota, FL, USA). Schaffer collateral inputs onto CA1 neurons were stimulated at 0.1 Hz with single shocks that each evoked single field excitatory postsynaptic potential (fEPSP) at stratum radiatum. There was no frequency potentiation at a stimulation rate of 0.1 Hz. At each stimulus intensity, six sweeps were averaged. The slope of evoked field potentials was measured at five different stimulation intensities and input–output (I/O) curves were constructed for different groups of animals. I/O profile was established by increasing the stimulus intensity and measuring the fEPSP slope. The lowest intensity that evoked a measurable response was chosen as the threshold intensity (T) and $2 \times T$ to $5 \times T$ were other tested intensities. Baseline recording was considered stable when the variation in the slope of fEPSP was less than 10%. After establishing a steady-state baseline response, stimulus intensity that evoked the fEPSP slope of approximately 50% of the maximum response was used (test-pulse). The average evoked field potentials were required to be stable for 30- min, before delivering tetanus. Animals with unstable baseline responses were discarded from the experiments. After stable baseline recording, LTP was induced using high frequency stimulation (HFS) protocol of 200 Hz (10 bursts of 15 stimuli, 0.2 ms stimulus duration, 10 s interburst interval) at a stimulus intensity that evoked a field EPSP slope of approximately 80% of the maximum response. fEPSP was recorded 60 min after the high-frequency stimuli. The slopes of fEPSP due to HFS were normalized concerning the 20-min baseline recording. The averaged response obtained during the 20-min baseline recording was applied as a reference point and was compared with the averaged response acquired during the 60-min post-HFS recording period. In this study, a 20% increase in slope is considered as a potentiation.

As described previously, paired-pulse stimulations with inter-pulse intervals (IPI) of 20, 80, and 200 ms were applied in all experimental groups to assess the short-term synaptic plasticity. The paired-pulse ratio (PPR) was computed as the fEPSP2/fEPSP1 slope and was presented as paired-pulse inhibition or paired-pulse facilitation (Hosseinmardi et al. 2011).

Data analysis

Six responses were averaged at each stimulus intensity level. The averaged waveform was used for further analysis. The field EPSP was determined from the averaged field potentials recorded from the stratum radiatum. A home-made assisted computer data analysis package was used to determine fEPSP slope (mv/ms) from the average field potentials. In the LTP experiment, the change percentage (%) in the slope of fEPSP was normalized concerning the 20-min baseline before HFS application. The averaged response obtained during the last 20-min baseline recording served as a reference and was compared with the averaged response acquired during the last 10-min of each recording period.

Statistical analysis

The Kolmogorov–Smirnov test (K–S test) was used for the analysis of normal distribution. Data were presented as mean ± SD and processed by commercially available

software GraphPad Prism® 6.0. In behavioral study, the data of the training trials (acquisition) were analyzed using a two-way analysis of variance (ANOVA) with days as repeated measures factor and treatments as between subjects' factor. For statistical analyses of probe and visibility trial data, unpaired *t*-test and one-way ANOVA were used. Two-way ANOVA and one-way ANOVA were followed by post hoc analysis (Bonferroni and Tukey's tests, respectively).

Two-way ANOVA and paired/ unpaired *t*-test were used for electrophysiological data analysis, with the differences being considered statistically significant at the level of $P < 0.05$.

Results

Behavioral results

Long-term treatment with acetylsalicylic acid-induced memory deficit

In this study, the animals were trained for 3 days and then they were able to find the location of the hidden platform. Escape latency was significantly declined [control rats: F (2, 18) = 19.30, $P < 0.001$, ASA-treated rats: F (2, 21) = 16.83, $P < 0.001$] after 3 days. Moreover, swimming distance decreased ($P < 0.001$, Fig. 2a) while swimming speed did not demonstrate any incredible change during training ($P > 0.05$, Fig. 2c).

Our data manifested a slower rate of memory acquisition in the MWM test in ASA-treated rats compared to

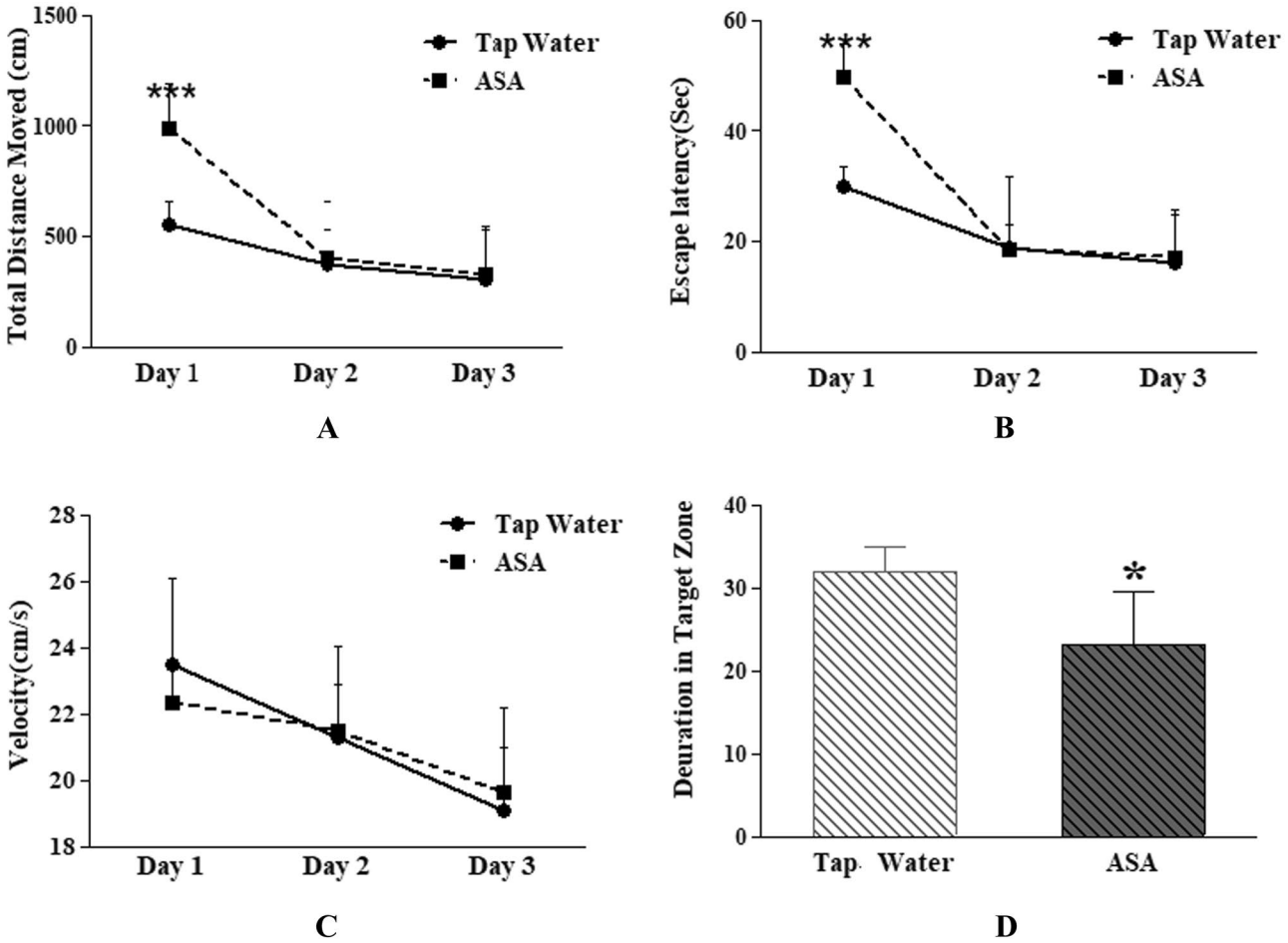

Fig. 2 The chronic low dose of acetylsalicylic acid (ASA) administration caused memory deficit. In the acquisition phase, ASA significantly increased the mean values of distance traveled to find hidden platform (cm) (**a**), escape latency (s) (**b**), but it had no effect on mean swimming speed (cm/s) (**c**) of the treated rats ($n = 7$). In probe test (**d**), it decreased time spent in the target quadrant on day 4. All data were expressed as mean ± SD. **a**, **b**, **c** Two-way ANOVA followed by Bonferroni's post-test. **d** Unpaired *t*-test, $^{*}P < 0.05$, $^{***}P < 0.001$. Stars indicate a significant difference from the control rats ($n = 8$)

the control group (those drinking tap water). ASA-treated rats showed longer traveled distances on the first day of training [F (1, 26) = 6.47, P = 0.0245, P < 0.001, Fig. 2a]. Additional analysis disclosed a significant increase in the escape latency on the first day [F (1, 26) = 7.17, P = 0.0190, P < 0.001, Fig. 2b] in animals treated with ASA compared to control group. As there were no differences in swimming speed (P > 0.05, Fig. 2c) between these two groups, the longer escape latency of the ASA-treated rats was due to impaired learning rather than locomotor defects. In the probe test, rats treated with ASA spent less time in the target quadrant zone (control rats: 32.00 ± 1.03 s, ASA-treated rats: 23.14 ± 2.41 s, P < 0.01, Fig. 2d). Escape latencies to find the visible platform during the visual discrimination task showed no significant differences between the experimental groups (P > 0.05, Fig. 4), which indicates no visual impairment in the animals.

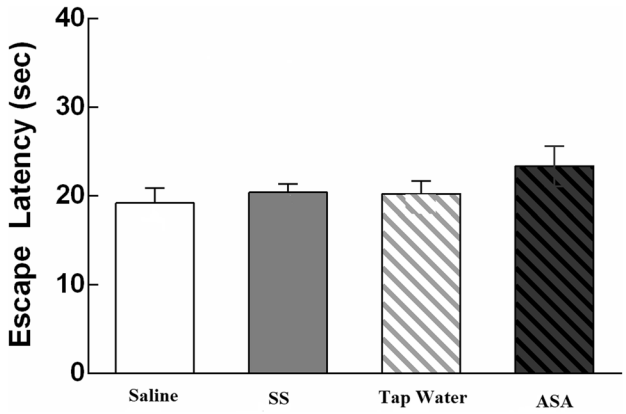

Fig. 4 Escape latency during visual discrimination task. Animals in all treatment conditions showed no difference in escape latency to find a visible platform. Data presented as means ± SD. One-way ANOVA, P > 0.05

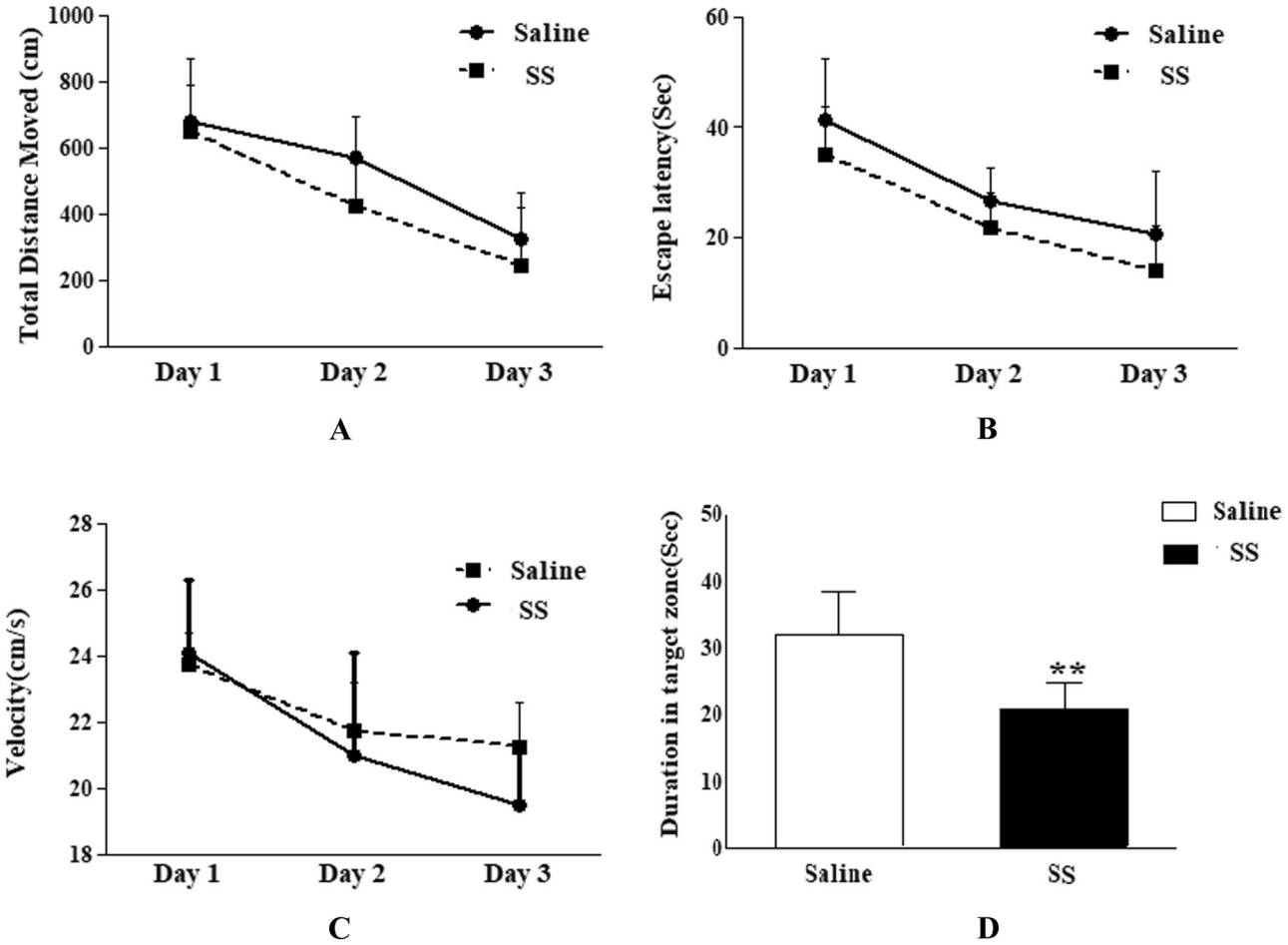

Fig. 3 Sodium salicylate (SS) impaired memory retrieval but not memory acquisition. In the acquisition phase, SS not affect the mean values of distance traveled to find hidden platform (cm) (**a**), escape latency (s) (**b**), and mean swimming speed (cm/s) (**c**) of the treated rats (n = 9). But, in the probe test (**d**), it decreased the time spent in the target quadrant on day 5 (**a**). All data were expressed as mean ± SD. **a**, **b**, **c** Two-way ANOVA. **d** Unpaired t-test, **P < 0.01. Star indicates a significant difference from control rats (n = 7)

Short-term treatment with sodium salicylate impaired memory retrieval but not acquisition

As mentioned in the "Materials and methods" section, SS-treated rats which received i.p. injections of SS six times before training, like the control group, learned the location of the hidden platform after 3 days of training. There were significant differences in swimming distance [control rats: F (1, 24) = 9.27, $P < 0.001$, SS-treated rats: F (1, 22) = 6.79, $P < 0.001$, Fig. 3a] and escape latency [control rats: F (1, 24) = 5.85, $P < 0.001$, SS-treated rats: F (1, 22) = 5.24, $P < 0.001$, Fig. 3b] after 3 days compared to the first day in both groups. Swimming speed did not reveal a remarkable change during training ($P > 0.05$, Fig. 3c).

SS administration increased swimming distance [F (1, 22) = 3.21, $P = 0.10$, Fig. 3a] and escape latency [F (1, 22) = 4.34, $P = 0.06$, Fig. 3b] but these effects were not significantly different. Interestingly, in the probe test, SS-treated animals spent significantly less time in the target quadrant zone in comparison to the control ones ($P^{<}0.05$, Fig. 3d). Escape latencies to find the visible platform during the visual discrimination task showed no significant differences between the experimental groups ($P > 0.05$, Fig. 4), suggesting no visual impairment in the animals.

Electrophysiological results

Baseline synaptic responsiveness

As the stimulus intensity increases, the slope of the fEPSP rises proportionally. Table 1 revealed that there was no statistically significant difference between the experimental groups in the mean values of stimulus intensity (T–5 T μA, $P > 0.05$, Table 1). I/O curves were prepared for each experimental group (Fig. 5). The differences in the mean values of the slope of fEPSP were not significant in the control and ASA-treated rats ($P^{>}0.05$, Fig. 5a). These data suggest ASA treatment did not alter baseline synaptic responses. However, a significant difference was observed in the baseline synaptic responses between saline- and SS-treated animals. SS administration decreased basal fEPSP slope [F (1.32) = 10.97, $P = 0.01$, 2 T; $P < 0.001$, 3 T; $P < 0.001$, 4 T; $P < 0.05$, Fig. 5b].

In all experimental groups, the mean values of baseline synaptic responses are demonstrated in Table 2. There was no significant difference between the experimental groups in the mean stimulus intensity (μA) required for evoking maximum response (I max) and 50% of the maximal response ($P > 0.05$, Table 2).

Acetylsalicylic acid and sodium salicylate changed short-term plasticity

To assess the impact of a sub-chronic high dose of SS and a chronic low dose of ASA exposure on hippocampal excitability at the circuit level, the paired-pulse stimulation paradigm was used at IPI of 20, 80, and 200 ms. ASA exposure significantly increased the PPR at 20-ms IPI (90.7 ± 1.6%) compared to the control group (76.1 ± 1.5%, $P < 0.05$, Fig. 6a) but did not affect the PPR at 80-ms and 200-ms IPI ($P^{>}$ 0.05). Besides, SS (125.9 ± 6.6%) remarkably increased the PPR at 20-ms IPI in comparison to the control group (76.3 ± 2.4%, $P < 0.05$, Fig. 6b).

Neither acetylsalicylic acid nor sodium salicylate affected LTP induction

LTP is considered as a molecular correlate of learning and memory. An LTP-inducing stimulus train was applied to SC afferents to CA1 neurons of all groups. To assess the effect of COX inhibition on LTP induction, LTP was measured in rats receiving SS or ASA. HFS could induce EPSP LTP in all groups ($P^{<}0.05$). But as shown in Fig. 7a and b, the percent of fEPSP slope potentiation in both ASA- and SS-treated rats was not different from their control groups ($P^{>}0.05$, Fig. 7a and b). Thus, statistical analysis manifested that COX-1 inhibition could not suppress LTP induction.

Table 1 The mean values of stimulus intensity T–5 T (μA in different experimental groups

Groups	T	2 T	3 T	4 T	5 T
Tap water	200 ± 0	400 ± 0	600 ± 0	800 ± 0	1040 ± 17.8
ASA	170 ± 4.4	340 ± 14.9	530 ± 16.2	720 ± 18.2	920 ± 18.2
Saline	190 ± 4.4	360 ± 17.8	560 ± 17.8	760 ± 17.8	960 ± 17.8
SS	150 ± 10	280 ± 16.7	450 ± 17.3	640 ± 17.8	840 ± 17.8

The lowest intensity that evoked a measurable response was considered as the threshold intensity (T) and 2 T to 5 T were other tested intensities. To compare multiple groups, the data were subjected to two-way analysis of variance. Differences were considered significant at the level of $P < 0.05$

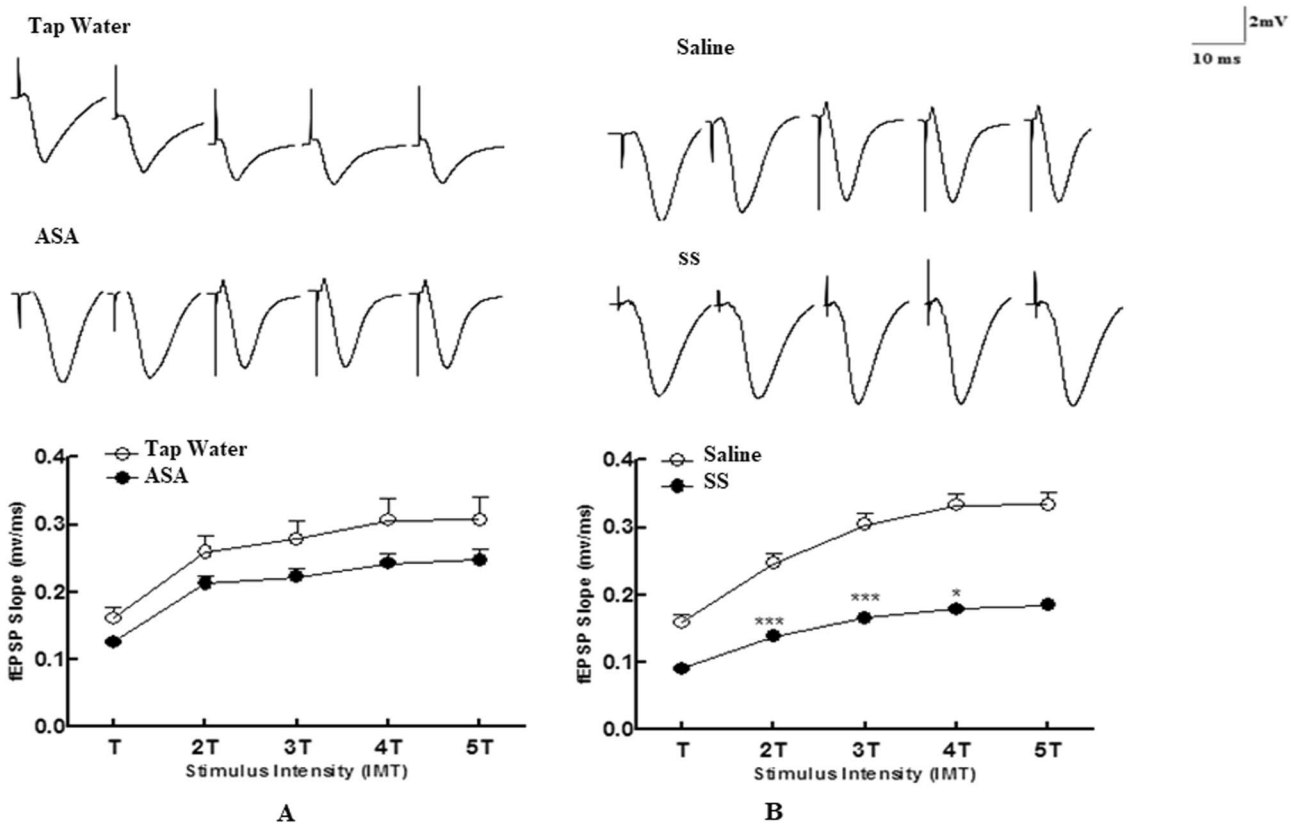

Fig. 5 The synaptic I/O relation between SC and CA1 pyramidal cells in (**a**), animals received acetylsalicylic acid (ASA) or vehicle (tap water) (**b**), and sodium salicylate (SS) or vehicle (saline), IMT, integer multiples of the threshold intensity (ANOVA followed by Tukey post-test, $n=5$, ***$P<0.001$, *$P<0.05$)

Table 2 The field responses recorded in the stratum radiatum of CA1 region of the rats which evoked upon single shock in Schaffer collaterals

Groups	[a]I_{max} (μA)	Max fEPSP slope (mV/mS)	[b]$I_{Test\ Pulse}$ (μA)	Test fEPSP slope (mV/mS)
Tap water	920 ± 45.6	0.26 ± 0.03	460 ± 8.9	0.12 ± 0.01
ASA	933 ± 13.6	0.25 ± 0.01	416 ± 9.1	0.12 ± 0.05
Saline	920 ± 18.2	0.23 ± 0.01	480 ± 8.9	0.11 ± 0.07
SS	950 ± 60	0.18 ± 0.01	420 ± 8.9	0.10 ± 0.02

The values are mean ± SD. There was no significant difference in the baseline parameters between different groups. To compare multiple groups, the data were subjected to two-way analysis of variance. Differences were considered significant at the level of $P<0.05$

[a]I_{max} is the stimulus intensity evoking the maximum response (Max fEPSP slope)

[b]$I_{Test\ Pulse}$ is the stimulus intensity that yielded 50–60% of the fEPSP slope (Test fEPSP slope)

Discussion

Two parallel studies were conducted to elucidate the effects of COX inhibitors on memory and synaptic plasticity. Our behavioral findings demonstrated that long-term administration of ASA but not short-term of SS impairs the acquisition phase of spatial memory. Despite the acquisition, the memory retrieval phase is disturbed by both short-term and long-term SS and ASA administration, respectively. Electrophysiological assessments revealed that ASA and salicylate affected the basal synaptic responses and short-term synaptic plasticity. Neither ASA nor SS affected LTP.

COX inhibitors, such as ASA and its main metabolite SS, are among the most widely used drugs in cardiovascular and pain prevention and treatment (Lipton et al. 2005). Growing pieces of evidence contrary to each other explained the effects of ASA and SS on spatial learning and plasticity. Some studies have reported improvement effect but some have suggested that they could lead to the impairment of spatial learning and synaptic plasticity (Smith et al. 2002; Hosseinmardi et al. 2011; Azimi et al. 2012; Gholami et al. 2015; Azimi et al. 2016; Niu et al. 2018).

It has been shown that the long-term administration of SS (200 mg/kg, twice a day for 7 or 14 consecutive days) impaired the abilities of acquisition, retrieval of spatial memory, and neurogenesis. Niu et al. also showed that

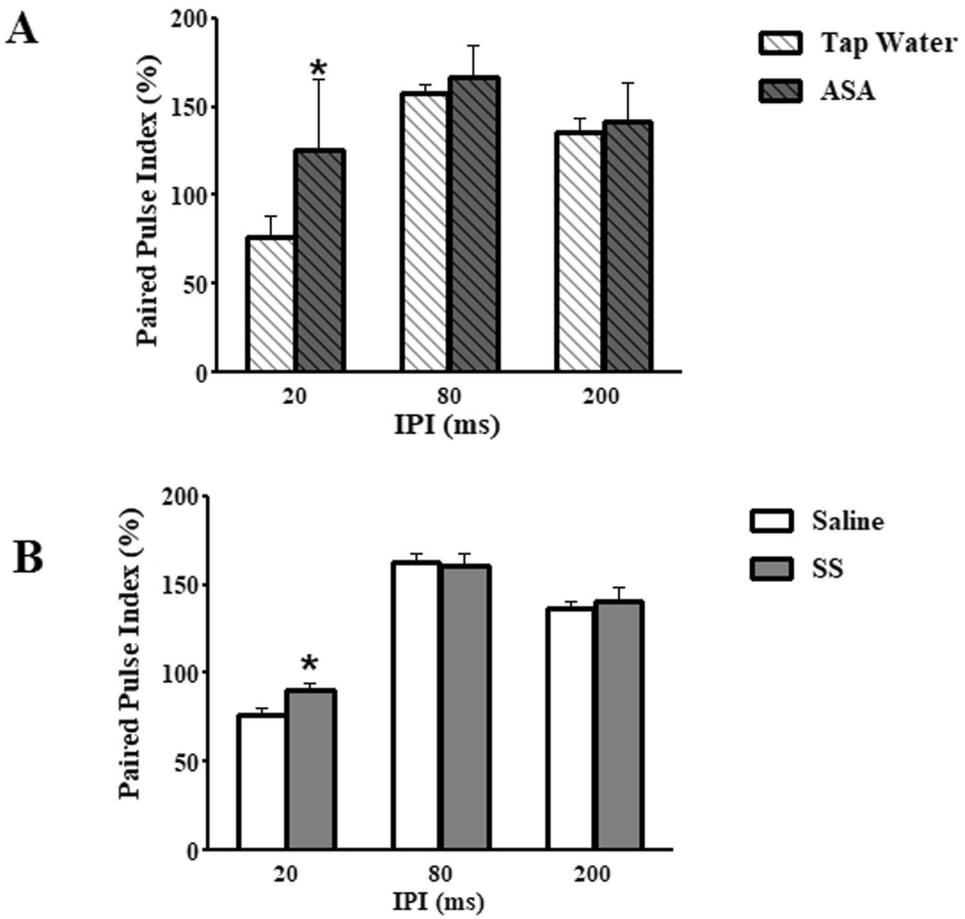

Fig. 6 The paired-pulse ratio at 20-, 80-, and 200-ms IPI in animals which received acetylsalicylic acid (ASA) or vehicle (tap water) (**a**), and sodium salicylate (SS) or vehicle (saline) (**b**). Bar graph represents mean ± SD. Unpaired *t*-test, $*P < 0.05$. Star indicates a significant difference from the control

following SS treatment, c-fos and delta-fosB protein expression in the CA1 region was inhibited after memory acquisition and memory retrieval, respectively (Niu et al. 2018). Considering that memory acquisition and retrieval requires c-fos or delta-FosB (Katche et al. 2010), decreased levels of these proteins following SS and ASA treatment may contribute to memory acquisition and retrieval impairments in the present study. Although the effect of long-term ASA administration on memory acquisition and retrieval and the effect of short-term SS on memory retrieval in our study are similar to the above-mentioned study, the lack of effect of SS on the acquisition phase may attribute to the duration of drug administration. It means that the effect of ASA and SS treatment depends on the dose and time which they are being used. It has been shown that salicylate has both stimulatory and inhibitory effects on neurotransmission. Decreased GABAergic inhibitory activity and increased glutamatergic stimulatory effect of SS have been postulated (Azimi et al. 2012). On the other hand, decreased PG function and cholinergic transmission following the SS administration which result in inhibitory effect (Sharifzadeh et al. 2005) might compensate for the SS stimulatory function. Therefore, in the present study, short-term administration of high-dose SS did not affect the acquisition phase. But it seems that time has a direct influence on the dominancy of the inhibitory effect and we observed impaired retrieval phase in SS-treated rats. Since the duration of ASA administration before training was longer than SS, the inhibitory effect was also seen during both acquisition and retrieval phases. Based on the obtained results, it seems that baseline COX activity is necessary for the acquisition, consolidation, and also retrieval phases of memory.

The electrophysiological study revealed that contrary to ASA, the SS administration decreased basal fEPSP slope. This pronounced decreasing effect of SS, as a metabolite of ASA, on the basal synaptic response, is probably related to the both higher administered dosage as well as the route of administration, i.e., i.p. injection of a higher dose of SS, versus to the oral administration of a lower dose of ASA. In other words, the possible lower bioavailability of ASA and its final lower concentration in blood circulation would lead to a low concentration of SS, which could not affect the basal synaptic response. In line with behavioral results, recording the baseline synaptic responses showed that the inhibitory effect of SS administration will be dominant.

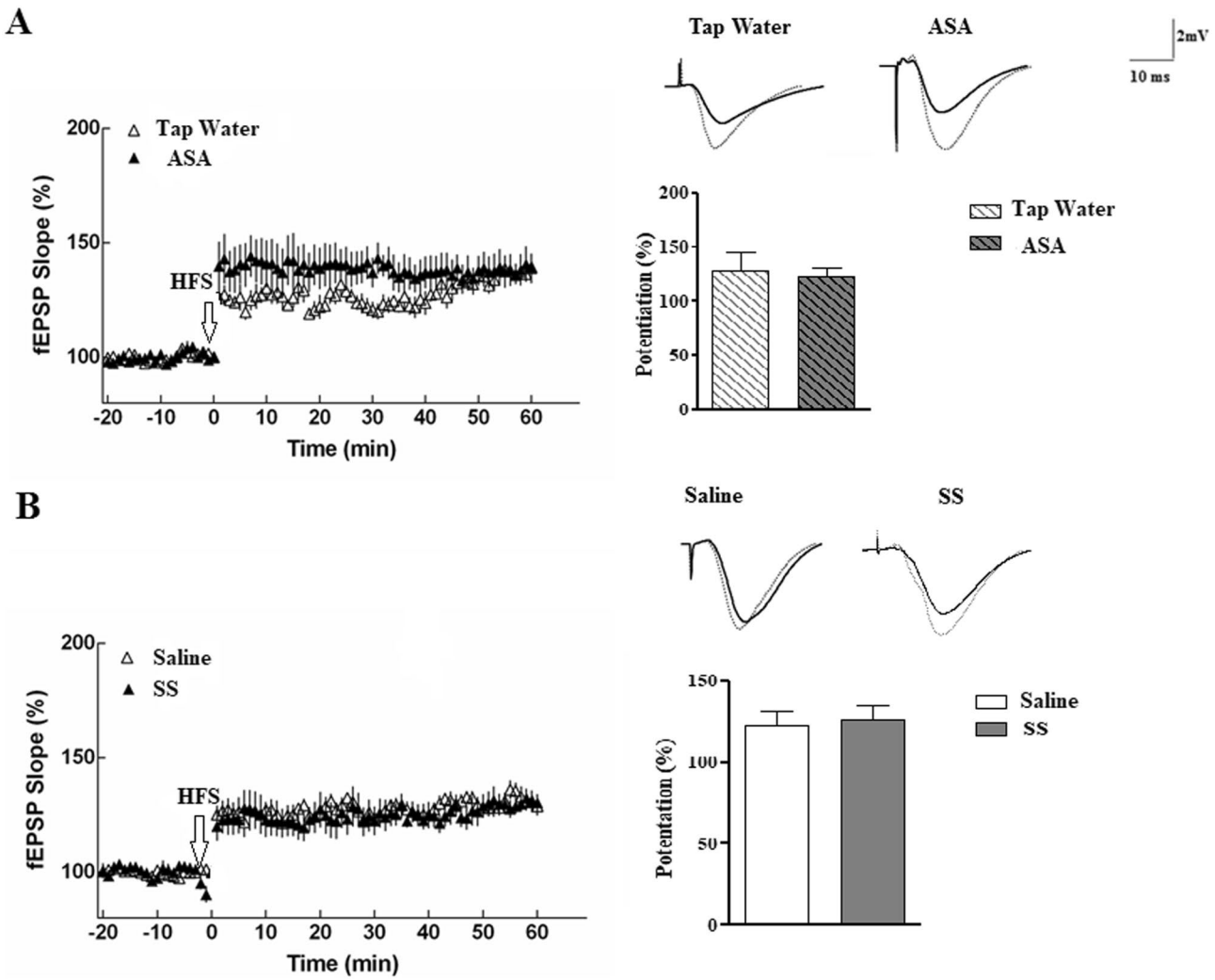

Fig. 7 Sub-chronic high dose of sodium salicylate (SS) and a chronic low dose of acetylsalicylic acid (ASA) exposure did not affect hippocampal LTP (**a**, **b**). The left panel shows fEPSP slope change (%) versus time following HFS in control and treated rats (ASA or SS). Insets: 1) Bar graphs show the average fEPSP slope change (%) during 60 min post-HFS; 2) Representative superimposed fEPSP slope taken at the baseline and during 60 min post-HFS. Bar graph represents mean ± SD. Calibration bar: 2 mV, 10 ms. One trace as a sample was shown. Unpaired *t*-test; $n = 5$, $P^{*}0.05$

In this study, to investigate the effect of SS and ASA on short-term synaptic plasticity, paired-pulse stimulation was used, which is a suitable way to evaluate the excitability of the hippocampal circuit. We found that ASA and SS exposure significantly increased the PPR at 20-ms IPI compared to the control group, but did not affect the PPR at 80-ms and 200-ms IPI. The regulation of synaptic plasticity in excitatory neurons vastly depends on the hippocampal GABAergic inhibitory system (Wagner et al. 2001). This system is the physiological basis of feed-forward and feedback mechanisms in the hippocampus (Andersen et al. 2006). The paired-pulse paradigm is disclosing the indirect testimony for the inhibitory strength in the hippocampus. IPI 10–20 ms assess $GABA_A$ (ionotropic CL- channels) and IPI 200 ms evaluate $GABA_B$ (G protein receptors coupled to K^+ channels activation) which have rapid and slow kinetics, respectively (Davies et al. 1990; Andersen et al. 2006; Dixon et al. 2014). In contrast, paired-pulse facilitation (PPF) can be seen in IPI 80 ms, due to an increased amount of neurotransmitter release (Santschi and Stanton 2003). Our results are in harmony with Sadegh et al. which showed that chronic treatment with salicylate leads to increasing PPR in IPI 10 ms (Sadegh et al. 2013). Since COX inhibitors reduce GABA transmission in the hippocampus, an increase in PPR in 20 ms is predictable. A previous study showed that the amplitude of spontaneous and miniature inhibitory postsynaptic currents (eIPSC and mIPSCs) was significantly reduced by SS, which is related to $GABA_A$ receptors (Gong et al. 2008). SS hyperpolarizes the resting membrane potential, which leads to reduce input resistance. Hence, SS

increases the excitability of neurons by inhibiting the activity of GABAergic neurons (Jin et al. 2015). Various studies revealed that presenting of extrasynaptic glycine receptors exerts a tonic inhibitory function in the hippocampus (Zhang et al. 2008; Xu and Gong 2010). Immunocytochemical studies have also shown that glycine receptors are widely expressed not only in hippocampal pyramidal neurons but also GAD (glutamic acid decarboxylase)-positive hippocampal interneurons which provide the equilibration in excitatory/inhibitory currents for proper hippocampal function (Brackmann et al. 2004). Glycine receptors as same as $GABA_A$ receptors are inhibitory ligand-gated chloride ion channel. It has been shown that SS in a non-competitive manner inhibits the a1-subunits containing glycine receptors (Lu et al. 2009). Hence, SS reduces the inhibitory currents not only as a consequence of $GABA_A$ receptor inhibition but also due to an allosteric modulation of glycine receptors.

Our data indicated that chronic administration of ASA and SS did not affect HFS-induced LTP. ASA through acetylation of serine 530 inhibits COX-1 (Roth and Majerus 1975; Lecomte et al. 1994). ASA inhibits COX-2 in the same manner but with less potency (Mitchell et al. 1993). It has been shown that inhibition of COX-2 but not COX-1 impedes the LTP induction and COX-1 inhibition did not affect LTP (Cowley et al. 2008). AA has preferential catabolism by COX-2 rather than COX-1. Hence, COX-1 produces less product than COX-2 in the equal AA presence (Swinney et al. 1997). COX-2 can regulate synaptic responses and plasticity. Previous studies suggested that acute COX-2 inhibition reduces HFS-induced LTP. NS398 (COX-2 inhibitor) suppressed LTP, and also long-term depression (Yang et al. 2008). The alteration of membrane input resistance and current threshold in slices pretreated with NS398 (COX-2 inhibitor) provides shreds of evidence that the basal activity of COX-2-generating PGE2 may dynamically regulate membrane excitability (Slanina et al. 2005). Probably, the lack of ASA or SS effect on LTP induction in the present study was due to the dominant effect of these drugs on COX-1 rather than COX-2. Besides, Chen et al. showed that CB1 cannabinoid receptors reduced basal excitatory transmission (EPSP). They showed the restrictive role of eCBs on LTP induction (Chen et al. 2002). Since COX-2 actively degrades eCBs (Kozak et al. 2004), and inhibition of this enzyme potentiates eCB signaling (Kim and Alger 2004), the absence effect of ASA or SS on LTP could be ascribed to different direct and indirect effects of COXs activity. Also, studies have been shown that PGE2 regulates membrane excitability in sensory neurons by modulating the K^+, Ih, and Na^+ current sensitive to TTX (Slanina et al. 2005). Hence, it is conceivable that COX inhibition can affect basal synaptic transmission and also LTP induction through different contrary ways. It also has been shown that in vivo chronic administration of salicylate results in increasing in PP1 (protein phosphatase 1) expression following HFS (Hosseinmardi et al. 2011). This enzyme has various functions due to controlling synaptic strength (Greengard et al. 1999). Its inhibition is necessary for LTP induction (Woo et al. 2002). It seems that SS and HFS coincidentally result in PP1 elevation which prevents LTP induction. On the other hand, eCBs destructing effect facilitates LTP induction. So, these different actions seem to cancel out each other in the present study and we did not observe any effect of ASA or SS on LTP induction. Our results about the effects of long-term low-dose (equivalent to prophylactic dose) and short-term high-dose (equivalent to analgesic dose) administration of ASA and SS on learning and memory and also plasticity were obtained based on behavioral and electrophysiological techniques. Our results confirmed that different protocols (dose and duration) of use of NSAIDs have different effects on memory formation and long-term synaptic plasticity. In future, determining the effects of these two protocols on plasticity biomarkers may be helpful to clarify the detailed mechanisms of their different effects on plasticity and behavior. As neurogenesis and dendritic spines are important components of structural plasticity, it was suggested to investigate neuroplasticity dynamically by evaluating neurogenesis and dendritogenesis.

Conclusion

Our data suggest that chronic administration of ASA may modulate the normal synaptic function and brain capacity. Despite the beneficial effects of acetylsalicylic acid, it needs to be used with increasing caution through monitoring the cognitive performances, especially during-long term treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00210-021-02092-4.

Author contribution NH and MJ designed and supervised the study and SH wrote the manuscript. MG, NS, and MD revised the manuscript. JD and SC conducted and analyzed experiments. All authors read and approved the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

Funding The authors would like to thank Dr. Fereshteh Motamedi for her technical support. We also would like to thank the Iran National Science Foundation (INSF) for its support (grant number: 91000228). We also gratefully acknowledge support from Shahid Beheshti University of Medical Sciences.

Data availability All data generated or analyzed during this study are included in this published article.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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