The aspirin metabolite salicylate enhances neuronal excitation in rat hippocampal CA1 area through reducing GABAergic inhibition

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Received 27 June 2007; received in revised form 17 October 2007; accepted 22 October 2007

Abstract

Salicylate is the major metabolite and active component of aspirin (acetylsalicylic acid), which is widely used in clinical medicine for treating inflammation, pain syndromes and cardiovascular disorders. The well-known mechanism underlying salicylate’s action mainly involves the inhibition of cyclooxygenase and subsequent decrease in prostaglandin production. Recent evidence suggests that salicylate also affects neuronal function through interaction with specific membrane channels/receptors. However, the effect of salicylate on synaptic and neural network function remains largely unknown. In this study, we investigated the effect of sodium salicylate on the synaptic transmission and neuronal excitation in the hippocampal CA1 area of rats, a key structure for many complex brain functions. With electrophysiological recordings in hippocampal slices, we found that sodium salicylate significantly enhanced neuronal excitation through reducing inhibitory GABAergic transmission without affecting the basal excitatory synaptic transmission. Salicylate significantly inhibited the amplitudes of both evoked and miniature inhibitory postsynaptic currents, and directly reduced γ-aminobutyric acid type A (GABA A) receptor-mediated responses in cultured rat hippocampal neurons. Together, our results suggest that the widely used aspirin might impair hippocampal synaptic and neural network functions through its actions on GABAergic neurotransmission. Given the capability of aspirin to penetrate the blood–brain barrier, the present data imply that aspirin intake may cause network hyperactivity and be potentially harmful in susceptible subpopulations.

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Keywords: Aspirin; Salicylate; GABAergic transmission; GABA A receptor; Hippocampus; Population spike

1. Introduction

Salicylate is the main metabolite and active component of aspirin (acetylsalicylic acid), which is perhaps the most widely prescribed medicine in the world. Sodium salicylate belongs to the family of non-steroidal anti-inflammatory drugs (NSAIDs). Its anti-inflammatory effects are mediated by the inhibition of cyclooxygenase and subsequent decrease in prostaglandin production (Kalgutkar et al., 1998; Vane and Botting, 1998). Another important application of aspirin and salicylate is the prevention of ischemic stroke and reducing the risk of cardiovascular events, which are also mediated by the cyclooxygenase inhibition (Sztriha et al., 2005). The anti-ischemic effects of salicylate also involve the inhibition of nuclear factor-kappaB transcription factor (NF-κB) (Frantz and O’Neill, 1995; Grilli et al., 1996; Kopp and Ghosh, 1994). Furthermore, aspirin and salicylate may have further public health potential by reducing the risk of cancer and Alzheimer’s disease (Vainio et al., 2002). However, salicylate also has many undesirable side-effects and toxicities, such as typical gastrointestinal irritation and bleeding, tinnitus, hypersensitivity, as well as some central nervous system (CNS) symptoms (Temple, 1978). Thus, an important issue is to identify the cellular and molecular targets of this drug in the CNS.

Recent evidence suggests that salicylate affects neuronal function through interaction with specific membrane channels/
receptors, such as voltage-dependent sodium, potassium as well as calcium channels. Furthermore, our previous study demonstrated that salicylate inhibited GABA<sub>A</sub> receptor (GABA<sub>A</sub>R)-mediated responses in cultured rat spinal neurons (Xu et al., 2005). However, the effect of salicylate on central synaptic and network activity remains poorly understood, although a few relevant studies are available, which focus on the auditory system. In inferior colliculus neurons, salicylate increased the neuronal spontaneous activity (Basta and Ernst, 2004). In the auditory cortex, salicylate could decrease the efficacy of inhibitory neurotransmission (Wang et al., 2006). Little is known about the effects of salicylate in the hippocampus, a key structure for many complex brain functions, such as exploration, cognition and memory. The hippocampus is also an important locus for many diseases, such as epilepsy, ischemia and Alzheimer’s disease. Salicylate can easily get through the blood—brain barrier and the cerebrospinal concentration of salicylate can reach several millimolars in animal models (Jastreboff et al., 1986). We therefore reasoned that salicylate might exert its effects in the hippocampus. To test this possibility, we studied the direct actions of salicylate on the synaptic transmission and neuronal excitation in hippocampal slices with electrophysiological recordings. Our results show that salicylate significantly enhanced neuronal excitation through reducing inhibitory GABAergic transmission.

2. Materials and methods

The care and use of animals in these experiments followed the guidelines of, and the protocols were approved by, the Institutional Animals Care and Use Committee of the Institute of Neuroscience, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences.

2.1. Hippocampal slice preparation

Transverse hippocampal slices (400 μm thick) were prepared form 14–21-day-old male Sprague–Dawley rats. After decapitation, the brain was removed and placed in oxygenated (95% O<sub>2</sub>/5% CO<sub>2</sub>) artificial cerebrospinal fluid (ACSF) at 4 °C. Slices were cut with a Leica VT1000S vibratome (Leica instruments Ltd., Wetzlar, Germany) and maintained at room temperature (23–25 °C) in a holding chamber filled with oxygenated ACSF for at least 1.5 h. Then a single slice was transferred to the recording chamber, where it was held between two nylon nets and continuously perfused with oxygenated ACSF (23–25 °C) at a flow rate of 2.5–3 μl/min. The same ACSF was used in cutting, incubation and recording, and contained (in mM): 119 NaCl, 2.5 KCl, 2.5 CaCl<sub>2</sub>, 1 NaH<sub>2</sub>PO<sub>4</sub>, 1.3 MgSO<sub>4</sub>, 26.2 NaHCO<sub>3</sub>, and 11 D-glucose, saturated with 95% O<sub>2</sub>/5% CO<sub>2</sub> (pH 7.4). The osmolarity of the ACSF was adjusted to 310–320 mOsm/L.

2.2. Hippocampal neuron culture

Cultured hippocampal neurons were prepared from E18 Sprague–Dawley rats. In brief, hippocampi were removed and treated with trypsin for 12–15 min at 37 °C, followed by gentle trituration. The dissociated cells were plated (60,000 cells/ml) on poly-L-lysine coated glass cover slips in 35 mm dishes. The plating medium was Dulbecco’s minimum essential medium (DMEM, Gibco BRL, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (Gibco) and 10% Ham’s F12 with glutamine (Gibco). Twenty-four hours after plating, the culture medium was changed to the maintenance medium containing Neurobasal Media and 2% B-27 supplement (Gibco), and then replaced every 3–4 days. Cultured neurons were used at 12–14 days in vitro.

2.3. Electrophysiological recordings

All electrophysiological recordings were performed at room temperature (23–25 °C) with an Axopatch-200B amplifier (Axon Instruments, Foster City, CA) and filtered at 5 kHz. Data were acquired and analyzed using a Digital interface and Clampfit 9.0 software (Axon Instruments). For extracellular recordings in the CA1 region of the hippocampus, a bipolar platinum–iridium stimulating electrode was placed in the Schaffer collateral axons to elicit field population responses. The field excitatory post-synaptic potentials (field EPSPs [fEPSPs]) and population spike (PS) were recorded via a glass micropipette filled with ACSF (1–3 MΩ) placed in the stratum radiatum and in the CA1 somatic layer, respectively (Fig. 1A). Stimuli (0.1 ms duration) were delivered every 30 s. Test pulses were recorded for 10–20 min prior to data collection to ensure stability of the response, and the amplitude of PS was controlled to be 1–2 mV. When the run-down of PS was significant, the data were not further analyzed. To examine the change of the recurrent GABAergic inhibition with PS recording, pairs of equivalent pulses were delivered at an interval of 50 ms, with the stimuli intensity sufficient to evoke maximal PS responses. The EPSP–Spikes (E–S) coupling curves were constructed by PS recording with various intensities of stimulation. To measure E–S coupling, the PS amplitude was calculated between the negative peak and a line drawn on the top of the two positive peaks (Fig. 1B). In the epileptiform wave, the first PS was measured (Fig. 3C). The fEPSP slope was calculated as the slope of the PS rising phase (Fig. 1B). The E–S curves were fitted with a sigmoidal equation \[ y = A_2 + (A_1 - A_2)/(1 + \exp((x - x_0)/\delta)) \] using Origin 7.5 software. The E<sub>50</sub> value was defined as the value of fEPSP slope at which the PS amplitude was 50% of its maximal response (Zhang et al., in press).

Whole-cell recordings were also made from the CA1 region of hippocampal slices at room temperature (23–25 °C). The neurons were visually identified using an upright microscope (BX51WI, Olympus, Japan) equipped with differential interference contrast (DIC) optics and an infrared camera. Patch pipettes were made from borosilicate glass (1.5 mm o.d.) with a micropipette puller (PC-830, Narishige, Tokyo, Japan). The internal pipette solution for voltage-clamp recording contained (in mM): 140 CsCl, 5 NaCl, 2 MgATP, 0.3 NaGTP, 0.1 ethylenediaminetetraacetic acid (EGTA), 10 N-2-hydroxyethylpiperazine-N0-2-ethanesulfonic acid (HEPES). The pH was adjusted to 7.2, and the osmolality was 300–310 mOsm/L. To block action potentials, 2 mM QX-314 was added into the pipette solution. The resistance of the patch electrode filled with above internal solution was 3–5 MΩ. Under voltage-clamp conditions, all the cells were held at −70 mV. Series resistances were usually 10–20 MΩ. To record miniature inhibitory post-synaptic currents (mIPSCs), GABA<sub>A</sub>-mediated currents were recorded in the current-clamp mode, resting membrane potential was determined by measuring the membrane voltage in the absence of current input. A series of 200 ms hyperpolarizing and depolarizing current steps (seven steps, ranging from −50 to +250 pA at +50 pA steps) were applied to the cell to determine repetitive AP firing properties.

Whole-cell GABA- and glutamate-induced currents were recorded in cultured hippocampal neurons at 12–14 days in vitro. The standard external solution contained (in mM): 150 NaCl, 5 KCl, 1 MgCl<sub>2</sub>, 2 CaCl<sub>2</sub>, 100
Fig. 1. Sodium salicylate induced EPSP-spike potentiation in rat hippocampal CA1 region. (A) Schematic diagram showing the arrangement of the recording and the stimulus electrodes in area CA1. A bipolar platinum-iridium stimulating electrode was placed in the Schaffer collateral axons to elicit field population responses. The field EPSP and population spike were recorded via a glass micropipette placed in the stratum radiatum and in the CA1 somatic layer, respectively. (B) Representative PS recordings showing that sodium salicylate increased the amplitude of PS in a concentration-dependent manner. Arrows indicate fEPSP slope and PS amplitude measurement, respectively. (C) Summary of the effects of SS ranging from 100 µM to 3 mM on the amplitude of PS (n = 7 for each group). The dashed line represents control response without SS treatment. **p < 0.01; N.S., no significant difference; ANOVA. (D) The plots from the representative recordings before, during and after SS treatment showing that SS (1 mM) caused a significant EPSP-spike potentiation by shifting the E−S curve to the left. The E−S curve was fitted with a sigmoidal equation using Origin 7.5 software. (E) Summary of E50 values obtained from E−S curves before, during and after SS treatment (n = 8 for each group). *p < 0.05; t-test.
3. Results

3.1. Sodium salicylate enhanced neuronal excitation in the hippocampal CA1 region

To study the actions of salicylate on hippocampal neurons, we examined the effects of salicylate on the field potentials recorded in the hippocampal CA1 region. Extracellular recordings were performed as shown in Fig. 1A. Sodium salicylate (SS) significantly enhanced the amplitude of PS in a dose-dependent manner ranging from 300 μM to 3 mM (Fig. 1B and C). To determine whether this enhancement in PS amplitude is due to the increased synaptic input or the enhanced ability of the EPSP to generate spikes, we further analyzed the change of EPSP-spike coupling following SS application. As shown in Fig. 1D and E, SS at 1 mM caused a leftward shift of E–S curve with the change of E50 from 0.50 ± 0.08 to 0.33 ± 0.06 mV/ms (n = 8, p < 0.05), indicating an E–S potentiation. This E–S potentiation was reversible after washout of SS (E50 = 0.55 ± 0.10 mV/ms, n = 8). However, SS had no noticeable effect on the basal fEPSPs as well as the input–output relationship of fEPSP (n = 7, p > 0.1, Fig. 2A and B), suggesting that synaptic input remained unchanged during SS treatment. Together, these results indicate that SS enhances the ability of EPSPs to generate action potentials, reflecting an increased neuronal excitation of CA1 neurons.

3.2. GABAergic transmission was a target of salicylate

To explore the mechanisms underlying the salicylate’s effects on neuronal excitation, we first examined the effects of SS on neuronal intrinsic excitability, which is crucial for neuronal excitation. However, after the blockade of both excitatory and inhibitory synaptic inputs, SS at 1 mM had little effects on the firing of action potentials induced by depolarizing current injection in CA1 pyramidal neurons (n = 11, p > 0.05, Fig. 2C and D). This result together with the finding that SS did not alter the basal excitatory synaptic transmission (Fig. 2A and B) suggests the possible involvement of GABAergic transmission. To test this possibility, we examined the effects of SS on the recurrent GABAergic inhibition with paired-pulse recordings (Fig. 3A). Two pulses with the maximal PS amplitude at an interval of 50 ms caused a significant paired-pulse inhibition (PS2/PS1, 0.65 ± 0.02, n = 15, Fig. 3A and B). This recurrent inhibition was significantly reduced by bath application of the GABA_A receptor antagonist picrotoxin (PTX, 10 μM) (PS2/PS1, 1.01 ± 0.01, n = 4, p < 0.01; Fig. 3B), consistent with a role of the recurrent GABAergic inhibition (Kandel et al., 1961; Papatheodoropoulos and Kostopoulos, 1998). Due to the marked epileptiform waves (Fig. 3C), we failed to perform the paired stimulation experiment in the presence of higher concentration of PTX (100 μM), preventing us to estimate the ratio of PS2/PS1 in the condition that recurrent GABAergic inhibition is completely abolished. Salicylate at a concentration ranging from 300 μM to 3 mM significantly reduced the paired-pulse inhibition (PS2/PS1, 0.71 ± 0.05, n = 7, p < 0.05; 1 mM, 0.80 ± 0.02, n = 8, p < 0.01; 3 mM, 0.85 ± 0.04, n = 7, p < 0.01; Fig. 3B), which recovered to 0.69 ± 0.02 (PS2/PS1, n = 5, data not shown) after washout of SS. This result suggests that SS reduces the recurrent GABAergic inhibition in hippocampal slices.

To further confirm whether GABAergic inhibition is a target of SS’s action, we examined whether GABA_A antagonist PTX can occlude SS’s effects on neuronal excitation. We used a high concentration of PTX (100 μM) to fully block GABAergic transmission in hippocampal neurons (Semyanov and Kullmann, 2002). As shown in Fig. 3C and D, PTX caused hyperexcitability with marked epileptiform PS and significantly reduced E50 of the E–S curve (changed from 0.50 ± 0.08 mV/ms [Fig. 1E] to 0.12 ± 0.03 mV/ms [PTX group, n = 4, Fig. 3D]). In the presence of PTX, SS (1 mM) failed to affect both the E–S curve and E50 (0.12 ± 0.03 mV/ms for PTX + SS group, n = 4, p > 0.1 compared with PTX group, Fig. 3D). Thus the SS’s action on neuronal excitation was completely occluded by PTX treatment. Taken together, these results suggest that a reduction of GABAergic inhibition is primarily responsible for the SS’s effect on the hippocampal neuronal excitation.

3.3. Salicylate reduced GABAergic transmission through a postsynaptic mechanism

The above findings with extracellular recording strongly suggest that GABAergic transmission is the target of SS in the hippocampus. We then examined the direct modulation of SS on the GABAergic synaptic transmission by using whole-cell recording from CA1 pyramidal neurons in hippocampal slices. We found that 1 mM SS significantly reduced the amplitude of eIPSCs from 447.41 ± 51.71 to 307.96 ± 38.28 pA (n = 8, p < 0.01, Fig. 4A and C). However, SS did not alter the input resistance of the neurons (269.41 ± 30.89 MΩ for the control group and 256.27 ± 24.94 MΩ for SS group, n = 8, p > 0.1, Fig. 4B).

To study whether a presynaptic or postsynaptic mechanism underlies SS’s inhibition on GABAergic transmission, we
further examined the effects of SS on the mIPSCs. As shown in Fig. 4D, SS (1 mM) significantly reduced the mIPSC amplitude (37.89 ± 1.84 pA for control group and 32.51 ± 1.59 pA for SS group, n = 13, p < 0.01) with a leftward shift of the cumulative probability plots (Fig. 4E), but had no significant effects on the frequency, rise time or decay time of mIPSCs. In general, the amplitude of mIPSC represents the postsynaptic properties while the frequency represents the presynaptic properties. Together, these results suggest that SS reduces GABAergic transmission in hippocampus through a postsynaptic mechanism.

3.4. Salicylate inhibited GABAA receptor-mediated currents in cultured rat hippocampal neurons

GABAA receptor is the main postsynaptic component of GABAergic synapse. Therefore, we directly examined the effect of SS on GABAA R-mediated current in culture rat hippocampal neurons using voltage-clamp configuration. Under the present experimental conditions, at a holding potential of -70 mV, we recorded a significant inward current with exogenous application of GABA at a concentration of 30 μM, which is close to the GABA concentration which induces half maximal GABAA response (EC50) (Schonrock and Bormann, 1993). This current could be completely blocked by 100 μM PTX or 10 μM bicuculline, another selective GABAA R antagonist (data not shown), indicating that the current was mediated by GABAA Rs. We found that SS significantly reduced the GABAA current in a concentration-dependent manner ranging from 300 μM to 3 mM (Fig. 5A and B). Sodium salicylate at 1 mM could inhibit GABAA response to 0.86 ± 0.02 of control (n = 9, p < 0.01, Fig. 5A and B). This effect was reversible after the washout of SS. Furthermore, the reduced GABA currents during SS co-application were totally abolished by 100 μM PTX (0.03 ± 0.01; n = 4, p < 0.01 compared with 1 mM SS group, Fig. 5B), confirming the specific effects on GABAA Rs. However, SS (1 mM) had no effect on the currents induced by glutamate at various concentrations.
(Fig. 5C and D), consistent with the finding that SS had no effect on fEPSP in hippocampal slices (Fig. 2A). These results reveal that SS specifically inhibits both GABA_A Rs and GABAergic synaptic transmission in rat hippocampal neurons, contributing to an overall reduction in the inhibitory strength which in turn impacts on the excitable state of the neuron.

4. Discussion

As the most commonly used drug, aspirin and its active component salicylate easily penetrate the blood–brain barrier, and the cerebrospinal concentration of salicylate can reach several millimolars in animal models (Jastreboff et al., 1986). With this concentration, we found that sodium salicylate significantly reduced GABAergic inhibition, leading to an increased neuronal excitation in the hippocampal CA1 area. To our knowledge, this is the first evidence that aspirin specifically regulates the synaptic and network activity in mammalian hippocampus.

Salicylate did not change the basal fEPSP, but dose-dependently increased the PS amplitude, which reflects an increase in the ability of the EPSP to generate spikes, a phenomenon also called as E–S potentiation, which always accompanies long-term potentiation but is also a consequence of decreased GABAergic inhibition within the hippocampal circuitry (Lu et al., 2000). Indeed, we showed that salicylate reduced the recurrent GABAergic inhibition. Furthermore, bath application of GABA_A antagonist, picrotoxin, completely occluded the effect of salicylate on E–S potentiation. All these results suggest that salicylate affects neuronal excitation through reducing GABAergic inhibition. Consistent with a previous study in the auditory cortex (Wang et al., 2006), both eIPSCs and mIPSCs in the hippocampal CA1 area were inhibited by salicylate, with no change in the input resistance. In addition, only the amplitude, but not the frequency of the mIPSCs was reduced. Furthermore, salicylate directly inhibited
Fig. 4. Sodium salicylate reduced GABAergic transmission in CA1 pyramidal neurons. (A) Typical traces showing that SS (1 mM) reduced the peak amplitude of eIPSCs. CNQX (10 μM) and D-APV (20 μM) were added to block glutamatergic responses. (B) SS did not alter the input resistance during recording (n = 8). (C) The amplitude of eIPSC was significantly reduced by SS (n = 8). (D) Representative recordings of mIPSCs before (upper panel) and during (lower panel) SS (1 mM) treatment. Besides CNQX and D-APV, 0.3 μM TTX was added to block action potential. (E, F) Cumulative probability plots of mIPSC amplitude (E) and inter-event interval (F) before and during SS treatment. Inset: the distributions of amplitude (E) and inter-event interval (F) before and during SS treatment. The distributions were fitted by a multiple Gaussian equation. *p < 0.05; N.S., no significant difference; Kolmogorov–Smirnov test. (G–J) Summary of the mIPSC amplitude (G), frequency (H), rise time (I) and decay time (J) before and during SS treatment (n = 13 for each group). **p < 0.01; N.S., no significant difference; r-test.
GABA<sub>A</sub>-mediated whole-cell currents in cultured hippocampal neurons to a degree similar to that of salicylate on the amplitudes of mIPSCs and eIPSCs. Thus we conclude that salicylate reduces the GABAergic transmission mainly through suppressing GABA<sub>A</sub>-mediated responses (Xu et al., 2005).

Interestingly, several other NSAIDs also modulate GABA<sub>A</sub>Rs (Halliwell et al., 1999; Sinkkonen et al., 2003). Therefore, it is likely that the GABA<sub>A</sub>R may be a common target for the actions of NSAIDs. However, we noted that a related NSAID, mfenamic acid modulated GABA<sub>A</sub>Rs in a subunit-dependent manner that only β1 subunit-containing receptors were inhibited by mfenamic acid, while β2 and β3 subunit-containing receptors were potentiated (Halliwell et al., 1999). In the hippocampus, where β2 and β3 subunit-containing receptors were abundant (Rabow et al., 1995), we found that salicylate inhibited GABA<sub>A</sub>R-mediated response, indicating a mechanism distinct from that of mfenamic acid. Although sharing a benzoic acid moiety in common with other NSAIDs, salicylate is a much simpler structure so may feasibly modulate the GABA<sub>A</sub>R via another binding site(s). Clearly, there is support for a similar inhibition of salicylate on GABA<sub>A</sub>Rs from auditory cortex and spinal neurons (Wang et al., 2006; Xu et al., 2005).

Salicylate as an active component of aspirin has many broad clinical applications and complex side-effects, while the hippocampal inhibitory GABAergic transmission is critically involved in many brain functions. A dramatic reduction in GABAergic inhibition will cause hyperexcitation, neuronal death and dysfunction, such as epilepsy (Ben-Ari and Holmes, 2005). In the auditory system, the effects of salicylate on neuronal excitation and GABAergic transmission have been implicated in salicylate-induced tinnitus (Cazals, 2000; Wang et al., 2006). The present study raises the possibility that the disturbance of hippocampal network activity by salicylate may also play a role in the development of tinnitus. In addition, a high risk for aspirin treatment is hemorrhagic stroke (Gorelick and Weisman, 2005). Other studies warned that salicylate may exacerbate neurodegeneration, and cause cerebral

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**Fig. 5. Sodium salicylate inhibited GABA<sub>A</sub>-mediated currents in cultured rat hippocampal neurons. (A) Sample recordings illustrating the reversible inhibition of SS on GABA-induced current. (B) Pooled data showing that SS inhibited GABA-activated current in a concentration-dependent manner (n = 6–9). The reduced GABA currents during SS (1 mM) co-application were totally abolished by 100 µM PTX (n = 4). The dashed line represents control response without SS treatment. *p < 0.05; **p < 0.01; N.S., no significant difference, compared with control; ##p < 0.01 compared with 1 mM SS group; ANOVA. (C, D) Typical traces and statistical results showing that SS had little effect on the currents induced by glutamate at various concentrations (n = 5–8). N.S., no significant difference; t-test.**
hemorrhage and cell death in various animal models of diseases (Najbauer et al., 2000; Quan et al., 2000).

However, we note that salicylate only modestly inhibited the GABAergic transmission. Under certain pathological conditions, GABAergic inhibition is largely reduced, resulting in the disinhibition of neural network, such as in brain ischaemia (Schwartz-Bloom and Sah, 2001), epilepsy (Ben-Ari and Holmes, 2005), and pain (Coull et al., 2003). Under such conditions, a slightly further reduction of GABAergic inhibition, as revealed in the present study by salicylate, might dramatically increase the neuronal excitation, causing drug-induced secondary damage. Therefore, for the clinical usage of salicylate in the treatment of patients with brain diseases associated with GABAergic disinhibition, the action of salicylate on GABAergic neurotransmission should be recognized. Interestingly, several neurodegenerative diseases, including Parkinson’s disease (Mallet et al., 2006) and Alzheimer’s disease (Lancot et al., 2004), as well as mental disorders such as schizophrenia (Lewis et al., 2005) and drug addiction (Liu et al., 2005a), are associated with an impairment of GABAergic neurotransmission. Given the pathogenic importance of network dysfunction in these disorders (Palop et al., 2006), the relationship between chronic intoxication by aspirin intake and neurodegenerative and/or mental disorders should be further explored, particularly during early stages of diseases and in susceptible subpopulations. Thus, the present findings may provide a synaptic mechanism for the aspirin-induced central side-effects.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (No. 30621062), the National Basic Research Program of China (No. 2006CB500803) and the Knowledge Innovation Project from the Chinese Academy of Sciences (KSCX2-YW-R-35). We thank Peng Jiang for technical assistance.

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