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Chronic sodium salicylate administration enhances population spike long-term potentiation following a combination of theta frequency primed-burst stimulation and the transient application of pentylenetetrazol in rat CA1 hippocampal neurons

Masoumeh Gholami [a], Farshad Moradpour [c], Saeed Semnanian [a], Nasser Naghdi [b], Yaghoub Fathollahi [a,*]

[a] Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[b] Department of Physiology, Pasteur Institute, Tehran, Iran
[c] Department of Physiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

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ABSTRACT

The effect of chronic administration of sodium salicylate (NaSal) on the excitability and synaptic plasticity of the rodent hippocampus was investigated. Repeated systemic treatment with NaSal reliably induced tolerance to the anti-nociceptive effect of NaSal (one i.p. injection per day for 6 consecutive days). Following chronic NaSal or vehicle treatment, a series of electrophysiological experiments on acute hippocampal slices (focusing on the CA1 circuitry) were tested whether tolerance to NaSal would augment pentylenetetrazol (PTZ)-induced long-term potentiation (LTP) and /or epileptic activity, and whether the augmentation was the same after priming activity with a natural stimulus pattern prior to PTZ. We noted an altered synaptic input-to-spike transformation, such that neuronal firing increased after a given synaptic drive. Population spike-LTP (PS-LTP) was increased in the NaSal-tolerant animals, but only when it was induced via a combination of electrical stimulation (theta pattern primed-burst stimulation) and the transient application of PTZ. Identifying and understanding these changes in neuronal excitability and synaptic plasticity following chronic salicylate treatment could prove useful in the clinical diagnosis or treatment of chronic aspirin-induced, or even idiopathic, seizure activity.

1. Introduction

Aspirin is the most widely used drug in the world, and salicylate is its main metabolite and active component (Sztriha et al., 2005; Vane et al., 1998). Their scope of pharmacological action is wide, and includes anti-inflammatory and anti-ischemic activity (Frantz and O'Neill, 1995; Grilli et al., 1996). Salicylate derivatives can also affect neuronal excitability in different brain areas through various ionic currents (Liu et al., 2007; Gong et al., 2008; Lu et al., 2011). In particular, several lines of evidence highlight the importance of the pro-seizure effects of salicylate derivatives. In addition, pretreatment of rats with non-steroidal anti-inflammatory drugs such as sodium salicylate (NaSal) and phenylbutazone converted the non-convulsant dose of pilocarpine to a convulsant one (Ikonomidou-Turski et al., 1988). Chronic exposure to salicylate derivatives produces tolerance to their analgesic effects (Pernia-Andrade et al., 2004; Sadegh et al., 2013). This form of drug tolerance, a result of adaptation in the brain, becomes apparent as a decrease in responsiveness and an increase in demand for the drug (Trujillo, 2002).

In some cases, drug tolerance and physical dependence are believed to be an aberrant form of synaptic plasticity that cause stable changes in synaptic strength, thereby altering learning and memory (Trujillo, 2000, 2002). At the gross anatomical level, the hippocampus is an essential structure for processing information related to learning and memory (Bliss and Collingridge, 1993; Morris et al., 2003), whereas at the cellular level, the steady forms of synaptic plasticity induced by patterned neural activity in the hippocampus, such as long-term potentiation (LTP) and long-term depression (LTD), are essential. Indeed, LTP and LTD are the synaptic parallels of, and the cellular experimental models for, learning and memory. The cellular and structural characteristics of

Abbreviations: aCSF, artificial cerebrospinal fluid; CA1, cornus ammonis 1; fEPSP, field excitatory postsynaptic potential; GABA, gamma-amino butyric acid; LTD, long-term depression; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate; PTZ, pentyleneterazol; PBs, primed burst stimulation; PS, population spikes; TPS, theta pulse stimulation; VDCC, voltage-dependent calcium channel

* Corresponding author.
E-mail address: fatolahi@modares.ac.ir (Y. Fathollahi).

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the hippocampus leave it especially vulnerable to many diseases which salicylates can exacerbate, including ischemia and epilepsy. For example, NaSal caused focal hemorrhage and cell death in the hippocampal formation and the entorhinal/piriform cortex of rats with kainic acid-induced seizures (Najbauer et al., 2000).

Pentylenetetrazol (PTZ), a gamma-aminobutyric acid (GABA) A receptor antagonist, is one of the most extensively used epileptogens (Psarropoulou et al., 1994). PTZ-induced seizures cause a number of seemingly permanent biological alterations in the hippocampus and other brain regions. These alterations may play an important role in synaptic plasticity (Qian et al., 1993). We have previously studied the effect of a brief PTZ application on the slope of field excitatory postsynaptic potentials (fEPSPs) and the amplitude of population spikes (PSs). In vitro, such an exposure (3 mM, 10 min) induced only transient potentiation of the fEPSP, but did induce a long-lasting enhancement of the PS amplitude (Omrani et al., 2000; Omrani and Fathollahi, 2003). Given the widespread use of salicylates in clinical practice and the relationship between salicylate tolerance, LTP, and hippocampal activity, we studied whether tolerance to NaSal would augment the potentiating and/or epileptogenic activity of a brief exposure to PTZ, and whether quantized priming via a natural stimulus pattern prior to PTZ exposure would change the lasting effects of PTZ.

2. Materials and methods

2.1. Animals and tolerance induction protocol

Male Wistar rats (120–150 g) were kept on a 12-h light/dark cycle with water and food available ad libitum. In accordance with the NIH Guide for the Care and Use of Laboratory Animals, every effort was made to reduce suffering and the number of animals used. To induce tolerance, NaSal (300 mg/kg, i.p) was injected once per day for 6 consecutive days (Pernia-Andrade et al., 2004; Sadegh et al., 2013). The anti-nociceptive ability of the drug was quantified to assess tolerance (Fig. 1), via a tail flick (TF, Harvard apparatus, 52-9495, US) test performed 20–30 min after each daily injection (Sadegh et al., 2013). They were selected according to the tail flick test. Control animals received the same pattern and number of saline injections.

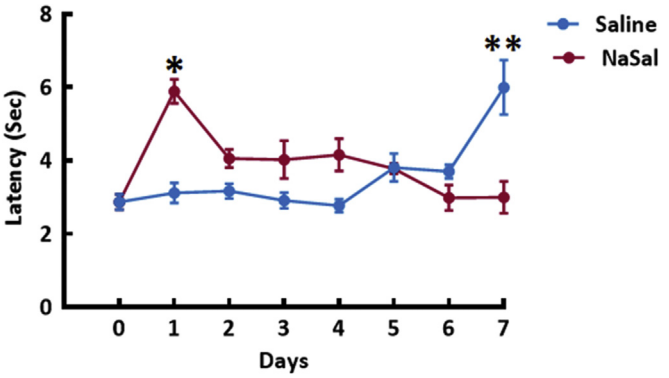

Fig. 1. Repetitive systemic sodium salicylate (NaSal) induces tolerance to the anti-nociceptive effects of NaSal. The latencies to tail flick (TF) were increased with NaSal injections relative to its baseline and the saline group ($F_{7,\ 47}=11.270$, $P<0.001$). This anti-nociceptive effect continuously decreased so that by day 6, the NaSal group ($n=4$) had the same latency to TF as its baseline (paired t-test, $P>0.05$) and saline ($n=4$, unpaired t-test, $P>0.05$). Interestingly, on the 7th day, TF latency was increased by a single dose of NaSal (300 mg/kg, i.p.) in the saline group (unpaired t-test, $^{**}P<0.01$). $^{*}P<0.05$, ANOVA followed by Bonferroni's multiple comparisons test (NaSal vs. saline).

2.2. Drugs

D,L-2-amino-5-phosphonovalerate (D,L-APV or APV) (Sigma, Gillingham, UK) and verapamil (Sigma) were both dissolved in artificial cerebrospinal fluid for application.

2.3. Electrophysiology

One day after tolerance was demonstrated in the tail flick test, rats were anesthetized with diethyl ether and decapitated. The brain was dissected from the skull and the right hippocampus excised. Transverse slices (430 μm) were cut with a vibratome (Campden Instruments, UK) in chilled artificial cerebrospinal fluid (aCSF), and then placed in a room temperature interface chamber for at least 60 min that contained aerated aCSF consisting of (in mM): NaCl, 124; $NaHCO_3$, 25; D-glucose, 10; KCl, 4.4; $MgSO_4\cdot 7H_2O$, 2; $NaH_2PO_4\cdot H_2O$, 1.25; and $CaCl_2\cdot 6H_20$, 2. Slices were then conveyed on a nylon mesh to a liquid/gas interface incubation chamber, where their undersurfaces were perfused with aCSF (32 °C) at a rate of 1–2 ml/min, while their upper surfaces were exposed to a humidified 95% O_2, 5% CO_2 gas mixture. The slices were maintained in this manner for one hour prior to recording.

fEPSPs and PSs were evoked by stimulation through a twisted pair of Teflon-coated stainless steel wires placed on the Schaffer collateral fibers. Synaptic responses were recorded using ACSF-filled micropipettes (4–8 MΩ resistance) placed in the stratum radiatum and stratum pyramidale of the CA1 portion of Ammon's Horn (Fig. 2). Schaffer collaterals were stimulated at 0.1 Hz with 200 μs constant-current square pulses delivered through the bipolar electrode. The baseline recording was considered stable when the variations in field potential amplitude or slope were less than ±10% for 20 min.

At the beginning of each experiment, an input/output curve was established, and we defined the brief PTZ challenge to be exposure of the slice to 3 mM PTZ for 10 min, followed by a washout period. The strength of the stimulus was adjusted to produce a response equal to 30–40% (for PTZ) and 50–60% (for primed-burst stimulation; PBs) of the maximum response. The final adjusted stimulus was considered the test pulse. For PTZ, the test pulse evoked the extra-spike free response needed to measure the slope of the fEPSP clearly. Baseline responses were recorded following the delivery of a test pulse every 10 s. A two channel microelectrode amplifier (DAM-80, World Precision Instruments, Sarasota, USA) was used to record the signals. Signals were amplified (1000 ×) and saved at a 10 kHz sampling rate on a personal

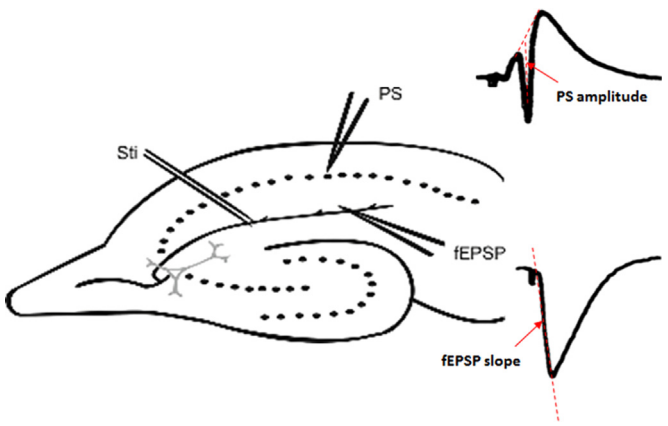

Fig. 2. A drawing shows the electrode positioning placed on the Schaffer collateral fibers as a stimulating electrode (Sti) and in the stratum radiatum or stratum pyramidale (as a recording electrode) of the CA1 portion of Ammon's Horn. A typical response at the stratum radiatum (fEPSP) and the stratum pyramidale (PS) of the CA1 region showing the measurements of fEPSP slope and the PS amplitude.