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DIFFERENCES IN STRIATAL SPINY NEURON ACTION POTENTIALS BETWEEN THE SPONTANEOUSLY HYPERTENSIVE AND WISTAR-KYOTO RAT STRAINS

T. L. PITCHER, J. R. WICKENS AND J. N. J. REYNOLDS*

Basal Ganglia Research Group, Department of Anatomy and Structural Biology, School of Medical Sciences, University of Otago, PO Box 913, Dunedin 9054, New Zealand

Abstract—The spontaneously hypertensive rat (SHR) and the Wistar-Kyoto (WKY) inbred rat strains display behavioral differences characterized by relative increases and decreases in levels of activity. Both strains have subsequently been utilized as animal models of hyperactive and hypoactive behavioral traits. The etiology of these behavioral characteristics is poorly understood, but may stem from alterations in the physiology of selected neural circuits or catecholamine systems. This study investigated the cellular properties of neurons from three genetically related strains: the SHR; WKY; and Wistar (WI). *In vivo* intracellular recordings were made under urethane anesthesia from spiny projection neurons in the striatum, a brain area involved in behavioral activation. Results obtained from 71 spiny projection neurons indicate that most cellular properties of these neurons were very similar across the three strains. However, the amplitude and half-duration of both spontaneously occurring and current-evoked action potentials were found to be significantly different between the SHR and WKY strains with neurons from the SHR firing action potentials of relatively greater amplitude and shorter duration. Action potential parameters measured from the WI rats were intermediate between the two other strains. These differences in action potentials between two behaviorally distinct strains may reflect altered functioning of particular membrane conductances.

Key words: SHR, WKY, striatum, urethane-anesthetized, intracellular recording.

The spontaneously hypertensive rat (SHR) was developed as an inbred strain to model aspects of human hypertension (Okamoto et al., 1972). During the selective breeding for high blood pressure, a number of behavioral characteristics were also fixed in the SHR genome. Some of these behavioral characteristics resemble those displayed in attention deficit hyperactivity disorder (ADHD) (Sagvolden et al., 1993, 1998). Interestingly, another genetically related strain, the Wistar-Kyoto (WKY) also displays abnormal behaviors and has subsequently been proposed as a model of depression (Pare, 1994; Malkesman et al., 2006). These strains are generally described as being hyperactive (SHR) and hypoactive (WKY), thus being at the opposite ends of the behavioral continuum.

The etiology of these behavioral anomalies is not known. However, some characteristics may be explained by alterations in dopamine functioning within the CNS (Viggiano et al., 2003). Alterations have been reported in both the SHR and WKY dopaminergic systems (Kujirai et al., 1990; Linthorst et al., 1991; Kirouac and Ganguly, 1993; Russell et al., 1995; Watanabe et al., 1997; Jiao et al., 2003; Mill et al., 2005). Whether a direct consequence of this altered dopamine function or not, differences in the physiology of brain areas involved in generating behavioral output could underlie the behavioral differences reported in these strains.

The basal ganglia is a neural circuit intimately involved in motor activity. The input nucleus of the basal ganglia, the striatum (caudate nucleus and putamen) receives extensive inputs from widespread areas of the cortex (McGeorge and Faull, 1989). Cortical information is processed in the striatum and output signals are sent via the spiny projection neurons to either the globus pallidus external segment (indirect pathway) or the globus pallidus internal segment (entopeduncular nucleus in rodents) or substantia nigra pars reticulata (direct pathway). Information is then relayed through the thalamus to the motor areas of the cortex. Information processing in the striatum is important for selection and initiation of motor sequences. Disruption of the striatal circuits, such as after the loss of dopaminergic inputs in Parkinson's disease or degeneration of striatal neurons in Huntington's disease, results in disorders dominated by motor abnormalities. Thus, variation in normal spiny projection neuron activity, mediated by alterations in cellular properties may also affect information flow through the basal ganglia and therefore, motor activity.

The present study utilized *in vivo* intracellular recording techniques to investigate the cellular properties of striatal spiny projection neurons in three rat strains: the SHR, a commonly used model of ADHD-like behaviors; the WKY, the normotensive genetic control for SHR and the standard albino Wistar (WI) strain. The purpose of the study was to investigate if there were, at the cellular level, physiological correlates to behavior.

EXPERIMENTAL PROCEDURES

Experimental subjects

Animals from the SHR, WKY and WI strains were obtained from the University of Otago Animal Facility (Dunedin, New Zealand).

*Corresponding author. Tel: +64-3-4795781; fax: +64-3-4797254.
E-mail address: john.reynolds@stonebow.otago.ac.nz (J. N. J. Reynolds).

Abbreviations: ADHD, attention deficit hyperactivity disorder; AHP, afterhyperpolarization; ANOVA, analysis of variance; SHR, spontaneously hypertensive rat; WI, Wistar; WKY, Wistar-Kyoto.

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These are maintained as inbred (SHR) and outbred (WKY and WI) colonies. The SHR and WKY are National Institutes of Health strains and were obtained from the Animal Resource Centre, Western Australia and have been maintained locally since late 2000. All surgical and experimental procedures were approved by the University of Otago's Animal Ethics Committee (97/01 and 93/04) as conforming to the New Zealand Animal Welfare Act (1999). All efforts were made to minimize the number of animals used and their suffering.

Animals were maintained in pairs or small groups on a reversed 12-h light/dark cycle with *ad libitum* access to food and water. The average age and weight of the animals on the day of experimentation was: SHR (n=23) 15.1±3.7 weeks and 320±33 g; WKY (n=21) 15.5±2.3 weeks and 308±24 g and WI (n=22) 10.8±2.1 weeks and 372±42 g. In general data were collected from one spiny projection neuron per animal, however in five animals (one SHR, two WKY and two WI) data were collected from two separate neurons per animal. SHR and WKY animals are known to weigh less than standard albino rats such as Sprague–Dawley at a similar age (Ferguson and Cada, 2003; Ferguson et al., 2003). Since efforts were made in the present study to record from rats in the weight range 300–400 g in accordance with our previous studies, there were significant differences in the ages of the SHR and WKY rats compared with the WI rats. Since all the animals used are considered in the adult age range, this difference is unlikely to have had a significant bearing on the results.

Stereotaxic surgery

On the day of experimentation animals were anesthetized with urethane (1.8–2.4 g/kg, i.p.; Sigma, Sydney, Australia) and fixed in the ear-bars of a stereotaxic frame. Core temperature was maintained at 36.5±0.5 °C with a homeothermic blanket and rectal probe. Local anesthetic (bupivacaine 0.5%; AstraZeneca, Auckland, New Zealand) was injected into the scalp and the skull exposed by a midsagittal incision. Burr holes were drilled in the skull for placement of an anchoring screw and an electrode over the right parietal cortex, contralateral to the recording site, in order to record the electrocorticogram. The electrocorticogram waveform was used as an indication of depth of anesthesia and supplementary anesthesia (ketamine 10 mg/kg and xylazine 2 mg/kg or urethane 0.6–0.7 g/kg; Parnell Laboratories New Zealand Ltd., Auckland, New Zealand) was given accordingly. A craniotomy was performed over the left striatum (AP; +8.5 to +12.5 mm, ML; +1.0 to +4.5 mm). Dental acrylic was used to secure the electrocorticogram electrode to the skull and to form a 'well' around the craniotomy. During recording the 'well' was filled with paraffin wax to maintain stability.

Cellular properties were compared in neurons recorded under urethane only and urethane with ketamine and xylazine supplement. There were no differences in cellular properties (data not shown); hence animals recorded under both anesthetic regimens are pooled.

Intracellular recording

Intracellular records from striatal spiny projection neurons were made with 1 M potassium acetate-filled microelectrodes (70–120 MΩ resistance) pulled from 3.0 mm diameter glass capillaries (Harvard Apparatus, Edenbridge, UK). Neuron impalement was aided by passing current pulses through the microelectrode. Neurons included in the study displayed a down-state membrane potential of at least −60 mV and had action potentials with amplitudes of greater than 50 mV, which overshot 0 mV. Spontaneous activity from each neuron was recorded (Fig. 1A) and neuronal responses to current pulses (Fig. 1 C) were collected at the onset of a down-state with the use of a threshold discriminator (Reynolds and Wickens, 2003). These responses were collected for measurement of the current/voltage relationships and basic action potential properties.

Measurement of cellular properties

The average membrane potential in both the down- and up-states of spiny projection neurons was estimated by fitting a weighted sum of three Gaussian curves to an all-points histogram constructed from a 30-s period of spontaneous activity (Fig. 1B). This method is similar to that described previously (Reynolds and Wickens, 2000). Input resistance of each neuron was estimated from the slope of a regression line fitted to subthreshold depolarizing current pulses (Fig. 1C and D).

Single action potentials were evoked by a 100 ms depolarizing current pulse triggered in the down-state (digitizing rate of 20 kHz). The intensity of the rheobasic current was set to ensure the firing of a single action potential, delayed by at least 50 ms. Action potential values were measured from all traces containing a single action potential. Parameters were measured as illustrated in Fig. 1E. Briefly, action potential threshold was defined as the point on the voltage trajectory when the rate of depolarization reached 8 V/s, using a moving window of 10 points to interpolate the slope. Action potential amplitude was defined as the distance from threshold to positive peak and action potential half-duration was measured at half-amplitude level. Action potential firing latency was measured from current pulse onset to the time of action potential threshold. Afterhyperpolarization (AHP) amplitude was measured as the distance from the threshold to the maximum negative peak occurring after the action potential. Parameter values for each neuron were an average taken from at least five single action potentials.

Average action potential traces were constructed by normalizing (to the time of action potential threshold) and averaging all traces containing a single action potential for each neuron. Group averages were then constructed from these individual neuron averages. Action potential depolarizing and repolarizing slope measurements were made on the average action potential traces from each neuron (Fig. 1F). All offline analyses were performed in Axograph 4.8 (Axon Instruments, Foster City, CA, USA).

Histology

Some neurons were passively filled during the recording period with Biocytin (4%; Sigma). Paraformaldehyde perfusion-fixed brains were sectioned on a vibratome (50 μm) and processed using standard histological techniques (Horikawa and Armstrong, 1988). Filled neurons were viewed under the light microscope.

Statistical analysis

Cellular property measurements of spiny projection neurons were compared using a one-way analysis of variance (ANOVA), with Tukey's B post hoc analysis. Significance was set at $P<0.05$.

RESULTS

Recordings were obtained from 71 neurons identified as spiny projection neurons on the basis of their electrophysiological properties. These properties are characteristic of spiny projection neurons reported previously by our laboratory (Reynolds and Wickens, 2004) and by others in the literature (Wilson and Groves, 1981; Mahon et al., 2001). Examples of spiny projection neuron morphology from each strain are shown in Fig. 2. There did not appear to be any obvious differences in morphology between neurons from the three strains, however, no quantitative analysis was carried out. Measurements of cellular properties from each of

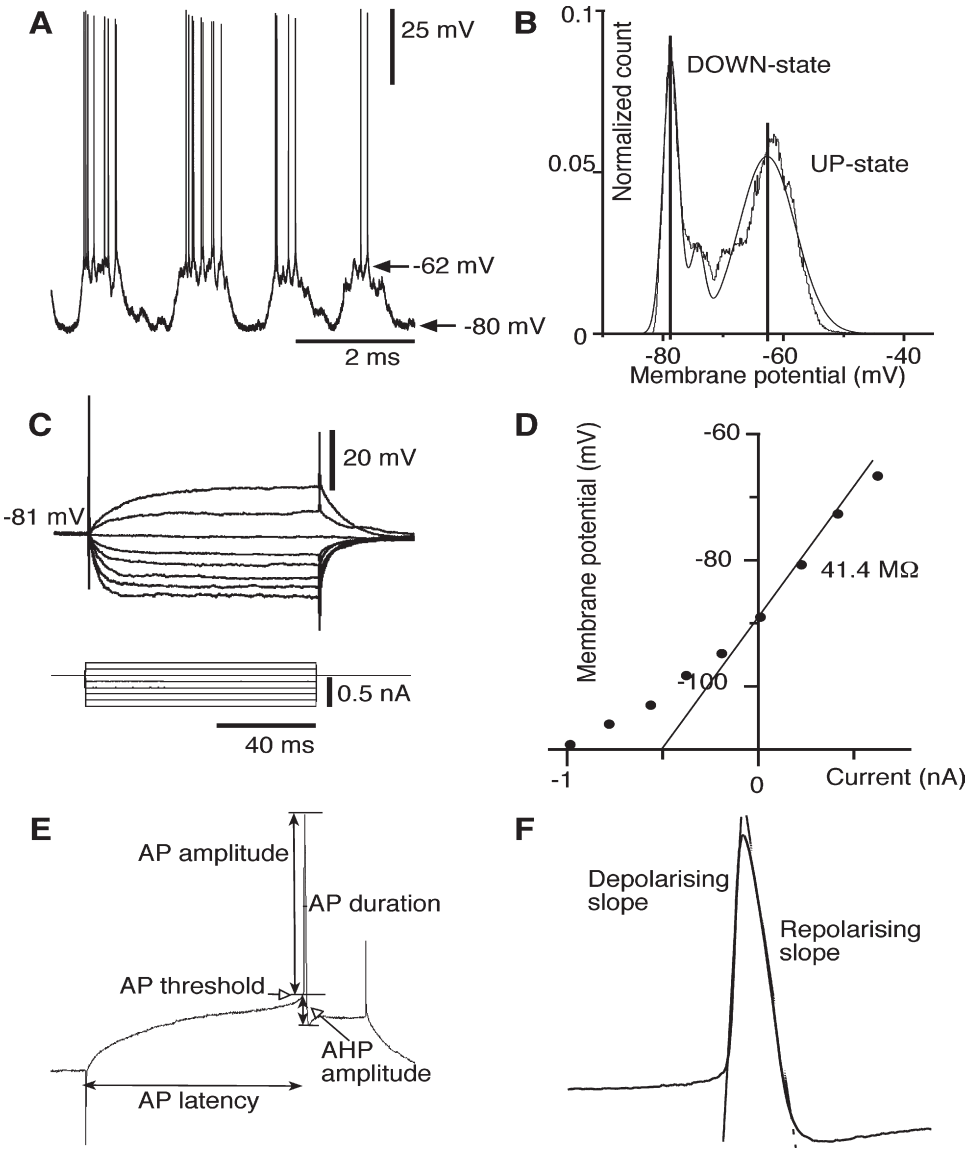

Fig. 1. Cellular property measurements in spiny projection neurons. (A) Short period of spontaneous activity recorded from a spiny projection neuron under urethane anesthesia. Note membrane potential fluctuations between hyperpolarized (down) and depolarized (up) states. (B) All-points histogram of membrane potential values during 30 s of spontaneous activity from neuron shown in A. Line represents the weighted-sum of three Gaussian curves fitted to the histogram to estimate membrane potential values. Membrane potential values for this neuron were down-state −80 mV, up-state −62 mV. (C) Subthreshold membrane potential (top) responses to intracellular current injection (below). (D) Plot of membrane potential responses to current injection shown in B. The slope of line fit between −0.1 and 0.4 nA was used as an estimate of the neurons input resistance. (E) Single action potential fired in response to intracellular current injection showing cursor positions for measuring individual action potential parameters. (F) Average action potential trace from one neuron on an expanded time-scale to indicate the position of the action potential depolarization and repolarization slope measurements.

the three strains are shown in Table 1. Most cellular properties were the same across the three genetically-related strains. However, there was a significant difference in action potential amplitude and action potential half-duration between the SHR and WKY strains ($P<0.05$; amplitude: $F_2=4.3$; half-duration: $F_2=4.0$; one-way ANOVA). Examples of individual current-evoked action potential from each strain are shown in Fig. 3A. Fig. 4A shows the average action potential traces for the SHR and WKY strains aligned at threshold, illustrating the significant difference in amplitude and half-duration. Average values for the action potential parameters recorded from WI rats were intermediate between the other two strains, and did not differ significantly from either. Notably the current required to evoke a single action potential delayed by at least 50 ms was similar in all three strains, as was the average input resistance for each group of neurons measured using depolarizing current pulses (see Table 1). The group current–membrane potential relation (Fig. 4 B) also did not reveal any differences between the strains in inward (current=−1.0 nA; $F_2=2.0$, $P=0.14$) or outward (current=+0.4 nA; $F_2=0.40$, $P=0.67$) rectifying directions.

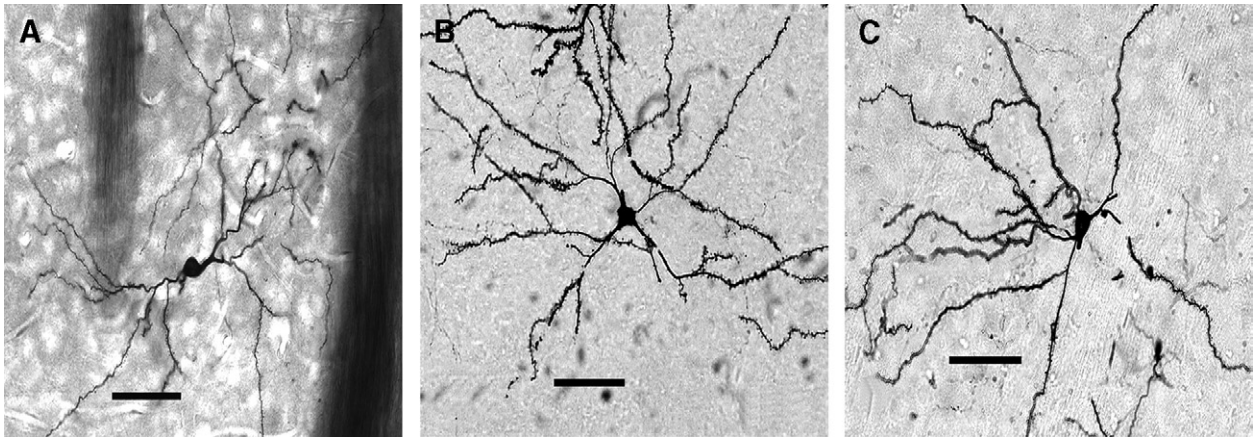

Fig. 2. Spiny projection neuron morphology. Individual examples of biocytin-filled neurons obtained within our laboratory from the three rat strains (A) WI, (B) SHR and (C) WKY. Note dark vertical lines on A are fiber bundles within the striatum. Scale bar=50 μm.

Action potential parameters (threshold, amplitude, half-duration and AHP) were also measured from action potentials spontaneously fired during an up-state. Amplitude and half-duration from spontaneously-evoked action potentials were also different between the SHR and WKY strains (Fig. 3B; action potential amplitude: SHR, n=21, 75.8±7.7 mV, WKY, n=15 69.3±7.4 mV, F_1=6.4; action potential half-duration: SHR 0.59± 0.11 ms, WKY 0.67±0.08 ms, F_1=5.0; P<0.05 one-way ANOVA). Consistent with findings from current-evoked action potentials, no other parameters from spontaneously-evoked action potentials differed between the strains. When current-evoked and spontaneously-evoked action potentials were compared within the SHR and WKY strains, there were no significant differences in the firing threshold, amplitude or half-duration (data not shown). There was, however, a significant difference in the AHP amplitude, with the spontaneously-evoked action potentials displaying smaller amplitude AHPs than the current-evoked action potentials in both strains (spontaneously-evoked AHP amplitude versus current-evoked AHP amplitude: SHR 8.5±2.9 mV versus 12.6±3.6 mV, F_1=18.2, P<0.0001; WKY 8.5±3.7 mV versus 11.6±3.1 mV, F_1=7.8, P<0.01; one-way ANOVA). Such a result is not unexpected, when taking into the account each mechanism used to reach the threshold for action potential firing. Up-states are due to prolonged coordinated barrages of activity in dendritically-located excitatory inputs from cortex and thalamus (Wilson and Kawaguchi, 1996), whereas we used relatively short current pulses injected into the soma, to produce a slow rising depolarization and a delayed action potential. The duration of preceding depolarization, the recent history of membrane potential changes and the voltage trajectory required to achieve threshold are all factors known to affect the AHP and excitability of spiny projection neurons by modifying the availability of intrinsic membrane conductances (Hernandez-Lopez et al., 1997; Wickens and Wilson, 1998; Mahon et al., 2000).

Table 1. Cellular properties of spiny projection neurons in three strains of rat

Cellular property	WI (n=24)	SHR (n=24)	WKY (n=23)
AP threshold (mV)	−52.1 (6.6)	−54.0 (6.4)	−51.0 (4.3)
AP amplitude (mV)	74.8 (8.1)	76.5 (7.5)*	70.1 (8.7)*
AP half-duration (ms)	0.63 (0.11)	0.60 (0.09)*	0.67 (0.06)*
AP firing latency (ms)	72.7 (11.1)	75.6 (10.8)	73.6 (11.7)
AHP amplitude (mV)	11.5 (3.1)	12.6 (3.6)	11.6 (3.1)
Current required to elicit single-delayed AP (nA)	0.72 (0.32)	0.68 (0.28)	0.79 (0.30)
Input resistance (MΩ)	38.9 (13.5)	41.2 (15.3)	36.8 (16.2)
DOWN state MP (mV)	−83.9 (9.7)	−85.9 (8.0)	−85.8 (7.6)
UP state MP (mV)	−68.5 (10.0)	−66.6 (8.6)	−68.1 (9.1)
Spontaneous action potential firing rate (Hz)	1.6 (2.1)	1.6 (1.8)	1.5 (2.1)

Values are means with standard deviations in parentheses. AP parameters correspond to those values obtained form current-evoked AP. Other cellular properties were measured from spontaneous traces or responses to current injection. AP, action potential; MP, membrane potential.

* P<0.05, one-way ANOVA.

The depth of investigation into the membrane conductances underlying the observed action potential differences that can be undertaken in a study such as this, using *in vivo* sharp-electrode recordings, is limited. Nevertheless we carried out an analysis in an attempt to begin to address this question. We measured the maximum slope, over 10 regression points, of both the depolarizing and repolarizing phases of the action potential (Fig. 1F). These parameters were measured from the average action potential traces constructed from each neuron.

On comparing the slope measurements between the SHR and WKY strains, there was no statistically significant difference in the rate of depolarization during current-evoked action potentials (SHR 188.1±26.2 V/s and WKY 174.9±23.8 V/s, F_1=3.3, P=0.08, one-way ANOVA). However, the repolarization slope was significant, indicating that the SHR shows faster repolarization rates following an action potential (SHR

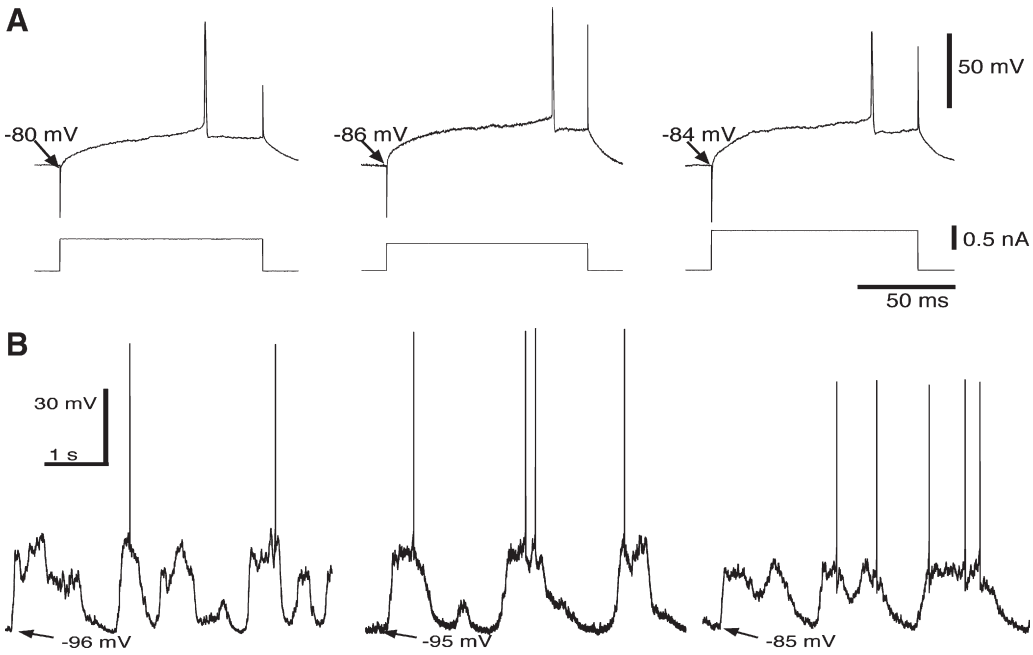

Fig. 3. Current-evoked and spontaneously fired action potentials from three rat strains; WI, SHR and WKY (left to right). (A) Representative examples of current-evoked action potentials. Membrane response (top) to intracellular current injection (below). Traces are aligned to the time of current pulse onset. (B) Representative examples of spiny projection neurons that were spontaneously active at a similar point during the experiment.

−108.4±14.1 V/s and WKY −98.9±17.4 V/s, $F_1=4.2$, $P<0.05$, one-way ANOVA). This increase in rate of repolarization is consistent with the SHR exhibiting on average a shorter duration action potential.

DISCUSSION

The present study utilized *in vivo* intracellular recording of spiny projection neurons in the dorsal striatum of three rat

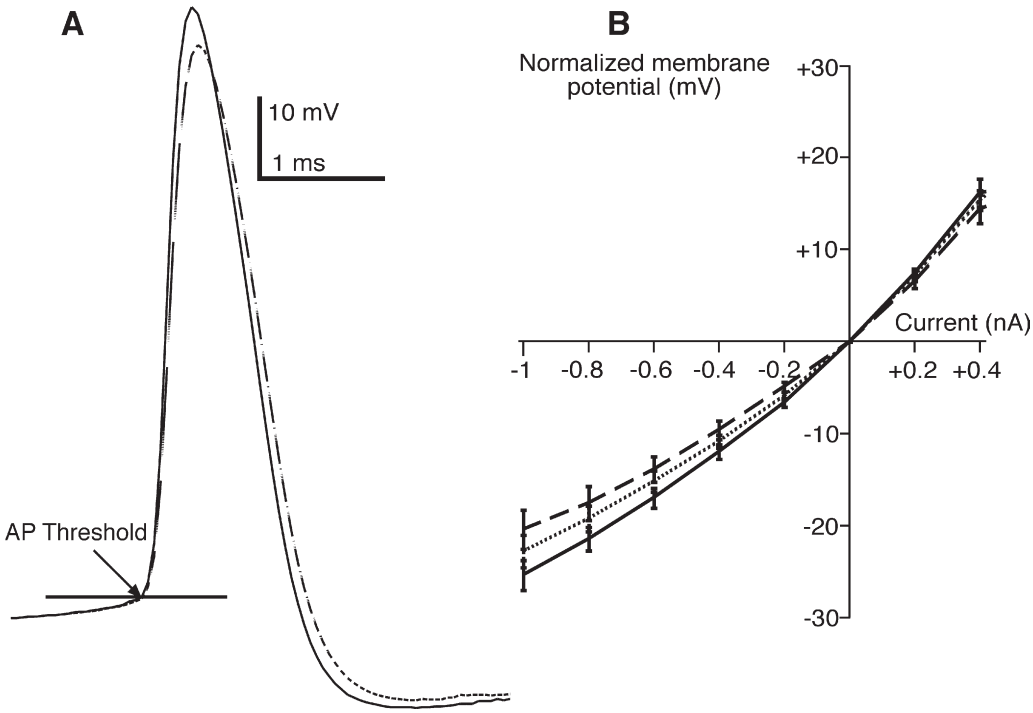

Fig. 4. (A) Average action potential traces aligned to threshold to illustrate significant differences in amplitude and half-duration. SHR, solid line, WKY, dotted line (WI excluded for clarity). (B) Group average current–membrane potential relation of all cells in each group. Each point is normalized to the membrane potential at zero current. SHR, solid line, WKY, dashed line, WI, dotted line.

strains, SHR, WKY and WI. These strains are of interest because the SHR and WKY have both been proposed as models of psychiatric disorders that have distinct behavioral characteristics. The SHR is proposed as a model of ADHD-like behaviors (Sagvolden, 2000; Sagvolden et al., 2005), while the WKY is proposed as a model of anxiety- and depression-like behaviors (Pare, 1994; Malkesman et al., 2006). These strains are genetically related as they were both derived from the common WI albino strain (Louis and Howes, 1990). It was therefore hypothesized that some electrophysiological differences between the strains might exist and explain, at least in part, some of the observed behavioral differences.

The results of this study indicate that the cellular properties of spiny projection neurons across the three strains are for the most part similar. The only differences detected were in the action potential amplitude and half-duration between the SHR and WKY strains for both current-evoked and spontaneously occurring action potentials. To the best of our knowledge, this is the first study to report the electrophysiological characteristics of neurons in the SHR and WKY strains using *in vivo* intracellular recording methods. In electrophysiological recordings, action potential amplitude can vary within cells from the same rat and in the same groups of animals, and can depend on electrode integrity and cell viability. However, our findings are made more convincing given the quality of the recordings (action potential amplitudes averaging $>$70 mV), the observation that both evoked and spontaneous spikes exhibited similar differences, and the fact that the control WI group showed intermediate amplitudes compared with the SHR and WKY rats.

Very little is known about the electrophysiology of neurons and neural circuits in the SHR and WKY strains. It is reported that post-tetanic potentiation in the dentate gyrus differs between the SHR and WKY strains and the level of potentiation is correlated with performance in the Morris water maze; SHR showed greater levels of potentiation and better maze performances than WKY (Diana et al., 1994). Thus, physiological differences in other brain circuits are present in these strains and might contribute to some of the behavioral differences.

Differences in specific action potential parameters observed in this study suggest that the SHR and WKY may display differences in certain membrane conductances that regulate these parameters. Such differences might be secondary to changes in striatal dopaminergic transmission, since alterations in the SHR dopaminergic system have consistently been described when compared with the WKY (Kujirai et al., 1990; Linthorst et al., 1991; Kirouac and Ganguly, 1993; Russell et al., 1995, 1998; Carey et al., 1998; Papa et al., 2002). In addition, genetic polymorphisms of components of the dopamine system have been positively associated with the ADHD phenotype (Faraone et al., 2005; Brookes et al., 2006; Li et al., 2006). Many of the spiny projection neuron membrane conductances are modulated by dopamine (Kitai and Surmeier, 1993; Surmeier and Kitai, 1993; Surmeier et al., 1995; Hernandez-Lopez et al., 1997). Therefore the above factors may be sufficient to influence conductances in the spiny projection neuron membrane and result in a difference in action potential parameters between the strains. Other neuromodulators such as serotonin and norepinephrine might also be involved in differentially modulating membrane conductances in the strains (McCarty et al., 1980; McKeon and Hendley, 1988; de Villiers et al., 1995), however it should be noted that the latter at least is likely to impact minimally on striatal function (Carlsson, 1959; Nicholas et al., 1993). It was not possible to investigate the effects of individual membrane conductances directly in this study, however, measurement of the slope of the depolarizing phase of the action potential suggested that differences are unlikely to be due to changes in sodium channel activation kinetics (Colbert et al., 1997; Frick et al., 2004). In contrast, the difference in the repolarization slope warrants further investigation into membrane conductances involved in membrane potential repolarization. Such an investigation would need to be carried out in an *in vitro* preparation utilizing patch-clamp techniques.

The present results were obtained using *in vivo* intracellular recording, which allows accurate measurement of action potential parameters to be made while preserving intact neural circuitry. Although these recordings were, through necessity, made in anesthetized animals, all groups were exposed to the same anesthetic conditions. Moreover, cellular properties were not changed by the use of different supplementary anesthetic regimens (data not shown). Hence, the differences in cellular properties between rat strains are not likely to be due to artifacts of anesthesia.

The observed differences are also unlikely to reflect differences in rheobasic current. Although there appears, in the representative example (Fig. 3A) to be a slight difference in amount of current required to evoke a single-delayed action potential for each strain, this was not significant as a group difference between the strains (Table 1). It is important to note that the amount of current for each neuron was selected to ensure that the firing of the action potential occurred within a similar time window for each neuron. In addition, there is no difference in the action potential threshold levels, which would be expected if the observed changes were a direct result of the rheobasic current. Similar strain differences in action potential parameters were found on measuring the spontaneously occurring action potentials. This also rules out the use of current to evoke action potential firing as a confounding factor in the observed differences.

What remains to be determined is the functional significance of the strain differences in action potential amplitude and half-duration. Notably, there were no differences in the baseline firing rates between the SHR and WKY strains as recorded from spontaneous traces (Table 1). However, firing rates are reduced under general anesthesia, so that a notable proportion of spiny projection neurons are silent (Wilson and Groves, 1981; Wilson, 1993; Wickens and Wilson, 1998). Hence accurate spike analysis between strains in a manner that is applicable to the

coherent patterns present during behavior is difficult in the present study (Stern et al., 1998).

Small changes in action potential duration can have significant effects on the magnitude of calcium influx into CNS synapses and the subsequent release of neurotransmitters (Sabatini and Regehr, 1997). Thus, if the action potential parameter differences recorded in the soma were also present in the nerve terminals, then the shorter duration of the SHR action potential could result in reduced calcium influx and therefore, reduced release of neurotransmitter from the terminals of spiny projection neurons. Firing of spiny projection neurons normally results in inhibition of their axonal target areas in the substantia nigra pars reticulata, globus pallidus and entopeduncular nucleus. Therefore, firing of the spiny projection neurons in the SHR would be expected to result in less inhibition of target areas than firing of spiny projection neurons in the WKY, for the same overall firing rate. This hypothesis would be best tested by simultaneously recording from spiny projection neurons and neurons of the basal ganglia output nuclei using single-unit or paired patch-clamp techniques. Only then could a firm conclusion be made on the behavioral significance of the strain differences in action potential parameters reported in this study.

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