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Regulation of dopaminergic function: an \([1^8\text{F}]\)-DOPA PET apomorphine challenge study in humans.

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Dopaminergic function has a key role in normal brain function, dopaminergic dysfunction being implicated in numerous neuropsychiatric disorders. Animal studies show that dopaminergic stimulation regulates dopaminergic function, but it is not known whether this exists in humans. In the first study (study 1), we measured dopamine synthesis capacity (indexed as \(K_i^{\text{m}}\)) to identify the relationship between baseline and change in \(K_i^{\text{m}}\) under resting conditions for comparison with effects of dopaminergic stimulation. In the second study (study 2), we used a within-subjects design to test effects of dopaminergic stimulation on dopamine synthesis capacity. In study 1, eight volunteers received two \([1^8\text{F}]\)-DOPA scans on separate days, both at rest. In study 2, 12 healthy male volunteers received two \([1^8\text{F}]\)-DOPA positron emission tomographic (PET) scans after treatment with either the dopamine partial agonist apomorphine (0.03 or 0.005 mg kg\(^{-1}\)) or placebo. In study 1, no significant correlation was found between baseline and change in dopamine synthesis capacity between scans \((r = -0.57, n = 8, P = 0.17, \text{two-tailed})\). In study 2, a significant negative correlation was found between baseline dopamine synthesis capacity and percentage change in dopamine synthesis capacity after apomorphine challenge \((r = -0.71, n = 12, P = 0.01, \text{two-tailed})\). This correlation was significantly different \((P < 0.01)\) from the correlation between baseline and change in dopamine synthesis capacity under unstimulated conditions. One-way repeated-measures analysis of variance showed a significant group \((\text{study } 1/\text{study } 2) \times \text{time interaction} (F(1,18) = 11.5, P = 0.003)\).

Our findings suggest that regulation of dopamine synthesis capacity by apomorphine depends on baseline dopamine function, consistent with dopamine stimulation stabilizing dopaminergic function. Loss of this autoregulation may contribute to dopaminergic dysfunction in brain disorders such as schizophrenia, substance dependence, and Parkinson’s disease.

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INTRODUCTION

Since its discovery in 1957,\(^1\) the neuromodulator dopamine has been shown to have a key role in regulating affect, attention, motivation,\(^2\) reward,\(^3\) sleep\(^4\) and voluntary movement.\(^5\) Variation in dopamine synthesis capacity (DSC) has been linked to alterations in a number of these functions\(^6,7\) and may have a pathoetiologial role in a number of neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD),\(^8\) Parkinson’s disease,\(^9\) schizophrenia\(^10,11\) and substance dependence.\(^12\) Specifically, elevated DSC, as measured by \([1^8\text{F}]\)-DOPA, is seen in people with schizophrenia\(^13,14\) and in the prodrome to psychosis,\(^15,16\) whereas DSC is reduced in ADHD\(^17\) and Parkinson’s disease.\(^18\) People with substance dependence also show alterations in DSC in some although not all studies.\(^19-21\)

Thus, determining the regulation of DSC is likely to be important for understanding and treating a number of brain disorders. Preclinical studies have shown that dopamine agonists at dopamine D\(_1\) and dopamine D\(_2\) receptors exert regulatory effects on DSC through three main mechanisms:

1. Terminal negative feedback, through presynaptic autoreceptors (mainly through D\(_2\) receptors), on dopamine nerve terminals in the striatum.\(^22-24\)

2. ‘Long loop’ negative feedback, involving a direct striatonigral pathway, stimulated by postsynaptic receptors and an indirect striatopallidal pathway, stimulated by postsynaptic D\(_2\) receptors.\(^25,26\)

3. Somatodendritic mechanisms, with dopamine acting on D\(_2\) receptors on dopamine cell bodies in the midbrain to decrease dopamine neural activity and release.\(^26,27\)

Apomorphine is considered a potent D\(_1\) and D\(_2\) receptor partial agonist (with higher selectivity for D\(_2\)), and is widely used for Parkinson’s disease.\(^28\) Preclinical studies suggest it is a partial dopamine agonist with 79% and 53% efficacy relative to dopamine at D\(_2\) receptor D\(_2\)-short and D\(_2\)-long splice variants, respectively.\(^29\) Besides acting on postsynaptic dopamine receptors, apomorphine has agonist effects on presynaptic autoreceptors,\(^30,31\) has been used to measure the distribution of dopamine autoreceptors,\(^32\) and has been shown to have effects on the basal firing rate of dopamine neurons,\(^33\) and differential effects on locomotor activity in rodents, depending on dosage.\(^34\) Apomorphine is therefore thought to act via one or more of the autoregulatory mechanisms above, to regulate dopamine function. Supporting this, a study in rhesus monkeys showed that apomorphine reduces DSC, and that this effect was greater in...
animals with greater baseline DSC.\textsuperscript{35} To date, in vivo studies in humans have been limited to people with Parkinson's disease (PD), one \textsuperscript{[\textsuperscript{11}C]}-raclopride study finding evidence of reduced dopamine release following amphetamine,\textsuperscript{36} and a study in early and late PD, finding reduced DSC in early PD, but the numerically opposite effect in late PD.\textsuperscript{37} The study of apomorphine in Parkinson's disease is problematic when looking at function in non-disease populations, as animal literature suggests autoreceptor sensitivity to be affected when damage to the nigrostriatal system has occurred.\textsuperscript{38}

Therefore, although these findings are consistent with an autoregulatory effect of dopamine agonism in disease, the regulation of DSC in healthy humans remains to be determined. In view of this, we aimed to determine the relationship between baseline dopamine synthesis capacity and the effect of dopamine stimulation, using apomorphine, on dopamine synthesis capacity, indexed using \textsuperscript{18}F-DOPA PET, in healthy humans. In study 1, we determined the reliability of \textsuperscript{18}F-DOPA imaging and the relationship between baseline DSC and change on re-scanning in untreated healthy volunteers to provide reference data for comparison. In study 2, we determined the effect of apomorphine on DSC using doses designed to preferentially act on presynaptic autoreceptors\textsuperscript{39} to test the hypothesis that apomorphine would alter DSC, and that this would depend on baseline DSC.

**MATERIALS AND METHODS**

Ethical approval

Study 1 was approved by the South London and Maudsley/Institute of Psychiatry NHS Trust. Study 2 was approved by the Hammersmith Research Ethics Committee. The Administration of Radioactive Substances Advisory Committee (ARSAC) granted permission to administer \textsuperscript{[\textsuperscript{18}F]}-DOPA for both the studies.

Participants

All the participants gave written informed consent. The participants were recruited through the local media. Inclusion criteria for all the subjects were: male gender, age 18–35, no history of major medical illness, and capacity to give written informed consent. The exclusion criteria for all the participants were: presence of any significant current medical disorder or treatment including history of head injury resulting in loss of consciousness and any neurological disorder; diagnosis of past or current psychiatric disorders using the Structured Clinical Interview for DSM-IV\textsuperscript{40} including alcohol or any other substance dependence or abuse. All the participants provided urine samples on the day of the PET scans to screen for drug use (Monitec HC12, Branan Medical, Irvine, CA, USA), and were excluded if they were positive. No subject was taking psychotropic medication at the time of study participation.

Study 1: test–retest study to determine the relationship between baseline dopamine synthesis capacity and change in dopamine synthesis capacity under resting (unstimulated) conditions

Eight healthy adults (mean age 23.6 ± 3.5 years, range 19–28 years, five males, six right-handed) participated in this study as part of an ongoing research project.\textsuperscript{41}

**PET data acquisition.** Each subject received two \textsuperscript{18}F-DOPA PET scans, administered approximately 2 years apart (mean ± SD = 113.6 ± 16 weeks). PET imaging was performed on an ECAT/EXACT3D:Siemens/CTI (Knoxville, TN, USA) PET tomograph (spatial resolution: 4.8 (0.2) mm; sensitivity: 69 cps Bq\textsuperscript{−1} ml\textsuperscript{−1}). High-resolution images of the whole brain were reconstructed from 95 planes with a section spacing of 2.425 mm. All the participants were asked not to eat or drink (except water), and refrain from alcohol for 12 h before the scan. In study 2, the imaging data were obtained on a Siemens CTI ECAT HR 962 PET scanner (Siemens, Erlanger, Germany) in three-dimensional mode. One hour before the scan, the participants received 400 mg Entacapone, a peripheral catechol-0-methyl-transferase inhibitor, and 150 mg Carbidopa, a peripheral aromatic acid decarboxylase inhibitor, to increase specific signal detection, as these compounds decrease the formation of radiolabeled metabolites that may cross the blood–brain barrier.\textsuperscript{33} The participants were positioned in the scanner with the orbitomeatal line parallel to the transaxial plane of the tomograph. The head position was marked and monitored and the movement was minimized using a head strap. The PET data were acquired in 32 frames of increasing duration over the 95 min scan (frame intervals: 8 × 15 s, 3 × 60 s, 5 × 120 s frames, 16 × 300 s).

**PET analysis**

For both the studies, image analysis was conducted as previously described (please see Supplementary Information).\textsuperscript{42} The striatal influx constant \(K_i\) was calculated compared with uptake in the reference region using a graphical approach adapted for a reference tissue input function.\textsuperscript{43}

**Statistical analysis**

The percentage change in \(K_i\) was calculated as: \(\text{baseline} \times 100\). For the purpose of analysis, ‘baseline’ refers to when subjects were not given apomorphine challenge, that is, when given either placebo or no compound. Statistical analyses were performed using SPSS (Version 21.0, IBM, Armonk, NY, USA). Significance was set at \(P < 0.05\) (two-tailed). Normality of distribution for \(K_i\) values and percentage change was assessed using the Kolgoroff–Smirnov test. In study 1, we determined the test–retest variability of repeat \textsuperscript{18}F-DOPA imaging as previously reported,\textsuperscript{44} and determined relationships between baseline \(K_i\) and difference between

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baseline and follow-up $K_{\text{cer}}$ using Pearson’s correlation. In study 2, within-subject differences baseline (placebo) and stimulated (apomorphine) conditions were assessed using paired $t$-tests. A Pearson correlation coefficient was computed to assess relationships between baseline $K_{\text{cer}}$ in the whole striatum and change with apomorphine.

Testing for regression to the mean
To test whether our results may represent regression to the mean, we conducted a one-way, repeated-measures analysis of variance to assess the effect of group (test-retest or apomorphine challenge) × change (change from baseline) interaction, with the hypothesis that partial agonist effects of apomorphine (change in $K_{\text{cer}}$ from baseline) would distinguish the apomorphine challenge group from that of the test-retest sample. In the analysis of variance, we used Levene’s test to test the null hypothesis that the variance of the two groups was equal. We also utilized linear regression to assess whether baseline $K_{\text{cer}}$ and the apomorphine × baseline $K_{\text{cer}}$ interaction could predict second scan $K_{\text{cer}}$. Finally, we tested the null hypothesis that there would be no difference in means and variances of both sets of measures (test-retest data set and those given apomorphine), and the correlation between the sets of measures would be equal. For this, we converted each correlation to a $z$-score, using Fisher’s $r$ to $z$ transformation. A $z$-score based on the difference between the two values and variance of the difference between the two scores was obtained.

RESULTS
Injected activity
Mean (s.d.) injected activity for Study 1 was 147.3 (6.6) MBq (scan one) and 147.7 (2.7) MBq (scan two). There was no significant difference in activity injected between both the scans ($t_{14} = 0.16; P = 0.88$). Mean (s.d.) injected activity for Study 2 was 149.0 (9.4) MBq (scan one) and 144.9 (5.5) MBq (scan two). There was no significant difference in the activity injected between both the scans ($t_{13} = 1.44; P = 0.18$).

Study 1: reliability of $^{18}$F-DOPA PET imaging and the relationship between baseline dopamine synthesis capacity and change over time in untreated people
There was no significant difference between scans (mean (s.d.) $K_{\text{cer}}$ values: scan 1 = 0.014 min$^{-1}$ (0.0015); scan 2 = 0.014 min$^{-1}$ (0.0014)).

The interclass correlation for both the scans was 0.834, as reported previously.

The relationship between initial $K_{\text{cer}}$ and change in $K_{\text{cer}}$ over time is shown in Figure 1. There was no significant correlation between initial $K_{\text{cer}}$ and change in $K_{\text{cer}}$ over time ($r = -0.57, n = 8, P = 0.17$; See Figure 1).

Study 2: the effects of apomorphine on dopamine synthesis capacity
The effect of apomorphine on dopamine synthesis capacity is shown in Figure 2.
There was no main effect of apomorphine on whole striatal $K_{\text{cer}}$ ($t_{11} = −0.71; P = 0.49$); mean (s.d.) $K_{\text{cer}}$ pre-apomorphine = 0.0120 (0.012) min$^{-1}$ and post-apomorphine = 0.0123 (0.0010) min$^{-1}$.

The mean (s.d.) difference (pre-apomorphine – post-apomorphine) for both doses was $−0.00025 (0.0013) \text{min}^{-1}$, mean (s.d.) percentage change = $−2.8\% (1.1\%)$.

The mean (s.d.) relative difference in dopamine synthesis capacity between baseline and post-apomorphine was $5\% (11\%)$ for $0.03 \text{mg kg}^{-1}$ and $2\% (10\%)$ for $0.005 \text{mg kg}^{-1}$.

There was no relationship between time between scans and change in $K_{\text{cer}}$ values (Spearman’s $\rho = −0.161, P = 0.62$, two-tailed).

To exclude a potential effect of apomorphine on blood flow in the reference region (cerebellum), we examined the reference region to see whether there was any change with administration of apomorphine. No difference in (as measured by the standardized uptake value at 95 min) was found ($t_{10} = 0.78, P = 0.45$).

Relationship between baseline $K_{\text{cer}}$ and percentage change. There was a significant negative correlation between baseline value and percentage change in $K_{\text{cer}}$ with apomorphine, $r = −0.71, n = 12, P = 0.01$ (two-tailed; See Figure 3). Removal of the outlier, identified in Figure 3, gave a correlation of $−0.9, n = 11, P < 0.01$.

This was larger, in absolute terms, in the subjects receiving the lower dose of apomorphine ($0.005 \text{mg kg}^{-1}$, $r = −0.87, n = 8, P < 0.01$), although the difference between the two dose ranges was not statistically significant.

There was no appreciable change in effect size or $P$-value when the two subjects who did not receive placebo were excluded from the analysis ($r = 0.67, P = 0.034$, two-tailed). There was no relationship between time between scans and change in $K_{\text{cer}}$ values (Spearman’s $\rho = −0.161, P = 0.62$, two-tailed).

Figure 1. $K_{\text{cer}}$ at baseline and follow-up, indicating no significant difference in dopamine synthesis capacity under rest conditions.

Figure 2. (a) Single-subject dopamine synthesis capacity at baseline and following apomorphine. (b) Mean (s.d.) dopamine synthesis capacity at baseline and following apomorphine.
DISCUSSION

Our main finding is that the regulation of DSC by a dopamine partial agonist depends on baseline DSC. Specifically, people with relatively high baseline dopamine synthesis show a reduction, whereas those with relatively low baseline values show an increase in DSC. This finding is consistent with apomorphine stabilizing DSC as a partial agonist. Partial dopamine receptor agonists increase dopamine receptor signalling if dopamine levels are low and decrease dopamine receptor signalling when dopamine levels are high as they compete with dopamine and given their lower intrinsic activity the net output is lower than dopamine per se. Moreover, we did not see a relationship between baseline dopamine synthesis capacity and change over time in our test–retest study, where there was no apomorphine administration, indicating that the effect seen with apomorphine is unlikely to be explained by regression to the mean.

Comparison with other imaging studies

Our findings extend those of an L-11C-DOPA study of rhesus monkeys, which also found a strong negative relationship between baseline Ki value and apomorphine induced change in Ki value (r = –0.93), to show this in humans.25 Our results are also similar to findings from an L-11C-DOPA study carried out in people with early- and late-stage Parkinson’s disease.37 Ekesbo et al.37 found a significant effect of stage of Parkinson’s disease on the effect of apomorphine such that patients with early-stage disease showed a reduction, whereas patients with late stage showed an increase in DSC in absolute terms, though this was not statistically significant. The patients with early-stage disease who showed a reduction with apomorphine had Ki values similar to those in our subjects who showed a reduction with apomorphine, whereas those with late-stage disease had low Ki values, lower in absolute terms than in our subjects, who showed an increase. Our findings thus extend these findings in non-human primates and Parkinson’s disease to indicate that the normal regulation of DSC also depends on baseline dopaminergic function.

Dopaminergic responses dependent on baseline dopamine

In addition to the studies discussed above, several other lines of evidence show this dependency on baseline dopamine function. In the Parkinson’s disease literature, animal and human studies have shown using functional magnetic resonance imaging increased the blood oxygen level-dependent activation in dopamine-deficient states, following apomorphine infusion.56–60 A human PET study, in early and advanced Parkinson’s disease, showed that response to L-DOPA was dependent on baseline status, with those with mild PD showing decreased striatal influx of L-DOPA, and those with advanced PD showing an increase in striatal L-DOPA uptake.61 A recent rodent study, examining the effects of aripiprazole (a partial dopamine agonist) on dopamine synthesis in rodents, finding that its effects on presynaptic D2 autoreceptors was either as an agonist or antagonist, depending on whether the experimental condition was of low or high dopaminergic tone.62 This finding has also been seen in healthy volunteers given the partial dopamine agonist aripiprazole or the dopamine antagonists haloperidol or risperidone.63–65

Mechanism of action

Our findings are consistent with evidence that apomorphine acts as a partial agonist at dopamine D2 receptors.29 This indicates that in healthy volunteers, with relatively high DSC and presumed relatively low-tonic auto-inhibition by dopamine, apomorphine will act as an agonist at autoreceptors, to decrease DSC. Conversely, in healthy volunteers with relatively low DSC and presumed relatively high tonic auto-inhibition by dopamine, apomorphine will compete with dopamine to occupy the autoreceptor. As apomorphine lacks the full agonist action, it will decrease the net functional agonist effect when it displaces dopamine, thereby causing increased DSC. This is in line with competitive binding studies.29 The data from CHO-expressed recombinant human D2S, D2L, D3 and D4 receptors measuring the influence of apomorphine on [35S]GTPyS binding both alone and in combination with dopamine points to it having partial agonist effects, as noted above.29 Nevertheless, it is important to note that partial agonism has not been shown in intact preparations, where apomorphine is generally found to behave as a full agonist, so this interpretation of our findings should be considered tentative at this stage.

Limitations

Our study was not intended to examine dose effects. Consequently, the sample size for the higher dose of apomorphine was small, which means that our analysis of dose effects lacks power and should be considered preliminary. It would be useful to use a wider dose range in future work to definitively test the dose effects. Our study design does not prove a causal relationship.
between baseline DSC and response to dopamine agonism. This could be done in preclinical experiments using optogenetic or other techniques to alter baseline DSC.

The test–retest comparison group had a longer duration of time between scans than the apomorphine challenge group. Despite this length of time, however, there was good test–retest reliability between scans in this group, and no evidence of regression to the mean. Nevertheless, it would be useful for future studies to test this over the same duration as used in the challenge group. It should also be noted that a few of the participants in the test–retest study showed large absolute differences, of –10% to 20%; although at the group level, the variability was much less. This likely reflects subject and scan acquisition-related variability, such as small movements of the subject during one scan session. However, this individual level variability would reduce our power to detect the relationship between baseline dopamine synthesis capacity and change under apomorphine. As such, it does not account for our findings, and could reduce the strength of the relationship.

Pharmacological considerations

Other considerations include possible effects of apomorphine on blood flow in the reference region (cerebellum), and the possibility that apomorphine could have effects on the peripheral elimination or metabolism of DOPA. However, these are unlikely to explain our results for the following reasons. First, we did not find differences in DOPA uptake in the reference region pre- or post-apomorphine. The consistency of 18F-DOPA activity in cerebellum at baseline and after apomorphine that we found would suggest that apomorphine is not having an effect on blood flow (please see Figure 1 and Supplementary Material). Nevertheless, further investigation using arterial blood sampling is needed to definitively exclude any significant alteration on blood flow by apomorphine at the dosage used in this study.

Although we were unable to test whether apomorphine would affect metabolism of DOPA in our sample, previous animal literature has failed to find any effect.75 Assuming an effect of apomorphine on blood flow, as shown in preclinical studies,66 this would have been uni-directional (either an increase or decrease compared with baseline conditions) and in contrast to our findings, which suggest bidirectional modulation of dopamine synthesis. Two subjects did not receive placebo during baseline scan, which may introduce an expectancy effect. However, taking these two subjects out of the analysis did not significantly change magnitude of effect size or P-value, as shown above. We accept that, in the subjects who reported side effects with apomorphine, breaking of the blind could have occurred. This could have potentially affected dopamine release in these individuals.67 It should be noted, however, that in those people receiving apomorphine at the lower dose (with no side effects) the results were unchanged, and magnitude of correlation was larger.

It is conceivable that, as $K_i$ is calculated from $K_i = \frac{K_1 \times k_3}{k_2 + k_3}$, which is a rectangular hyperbola, if $K_i$ is higher, a change in $k_3$ will have different effects on $K_i$ than when $K_i$ is lower. We therefore ran a simulation using standard values for $K_1$, $k_2$ and $k_3$.68 We do not know the real change in $k_3$ but around control values the relationship between $K_i$ and $k_3$ is not exactly linear. Assuming a +30% change in $k_3$, this would translate into a +33% change for subjects with the largest $K_i$, and in a +40% change for those with the lowest $K_i$. Therefore, it is unlikely that our results reflect a statistical artefact. It could also be hypothesized that the conversion rate, $k_3$, may be saturable, and therefore one would not see a change in those with higher baseline $K_i^{cer}$. However our results argue against this. In our study, similar changes were seen in those with both high and low baseline $K_i^{cer}$, in keeping with other pharmacological studies using the F-DOPA ligand, which have shown a decrease in $K_i^{cer}$ in those with relatively higher baseline $K_i^{cer}$.63,69 Furthermore, in normal conditions, AADC is not the rate-limiting step in dopamine synthesis and apomorphine at the doses used in the study is not known to directly influence AADC levels, but modifies it functionally via dopamine receptors.70 In these conditions, tracer quantities of 18F-DOPA will not saturate AADC. However, it should be noted that AADC may be saturable when high doses of L-DOPA are given, for example, as a treatment for Parkinson’s disease. Finally, it is worth examining the possible acute and chronic effects of apomorphine. Animal work suggests differential effects of apomorphine acutely (with a decrease in striatal dopamine turnover with acute treatment, and an increase with chronic treatment).71 In humans, chronic treatment with D2 partial agonists with high intrinsic activity, aimed at selectively engaging the autoreceptors, has not been effective in treating schizophrenia.72 The main reason attributed has been desensitization of D2 autoreceptors. However, animal literature is mixed in this regard.73,74

Therapeutic implications

Our finding that low-dose apomorphine has a stabilizing effect on dopaminergic function has implications for the treatment of a number of disorders in addition to Parkinson’s disease. In schizophrenia, where DSC is predominantly elevated,13,14,73,74 our findings indicate that a low level of dopamine agonism may act to reduce elevated DSC. The low dose used suggests there will not be significant postsynaptic effects, reducing the risk of exacerbating psychosis or other side effects. Indeed, there is evidence of efficacy of apomorphine in schizophrenia, although initial positive results75 were not replicated,72 possibly because doses used in some studies were higher (up to 6 mg) than those we used, as well as desensitization, as noted above. Dopamine agonism could also have a role in substance dependence (particularly stimulant dependence) to stabilize dopaminergic neurotransmission by potentially providing tonic dopaminergic stimulation and reducing surges in dopamine associated with drug-related cues. Our findings support studies in these conditions to determine the effect of dopaminergic stimulation on dopamine function.

CONFLICT OF INTEREST

ODH has received speaker bureau honoraria and charitable research funding from AstraZeneca, BMS, Eli Lilly, Jansenn-Cilag and Roche. The work of ODH has been funded by the Medical Research Council, UK and Wellcome Trust. SK has received grant support from AstraZeneca and GlaxoSmithKline and has served as consultant and/or speaker for AstraZeneca, Bioline, BMS-Otsuka, Eli Lilly, Janssen (J&J), Lundbeck, NeuroSearch, Pfizer, Roche, Servier and Solvay Wyeth. The remaining authors declare no conflict of interest.

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