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Are Changes in the Wnt/β-Catenin Pathway Involved in Cocaine and Stress-Induced Long-Term Neuroadaptations?

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Abstract

Drug addiction has been defined as a chronic relapsing brain disease, characterized by compulsive drug seeking and use, despite harmful consequences. This phenomenon has been extensively studied and the use of animal models has contributed to elucidate neurobiological bases of the different stages in the addiction process. For the past years, we have been studying the role of the Wnt (Wingless-related integration site) pathways in cocaine-induce neuroadaptations by using the behavioral sensitization paradigm to model addiction-like behaviors. The Wnt pathways are critical during the development of both the central and peripheral nervous systems. In particular, we centered our attention on the Wnt/β-catenin or canonical pathway. This pathway mediates the stabilization and nuclear translocation of the final effector β-catenin, where it can promote the expression of different target genes. Our findings reveal a specific spatiotemporal participation of the Wnt/β-catenin pathway in cocaine-induced behavioral sensitization. We found that while the initiation or development of sensitization involves an inhibition in the Prefrontal Cortex's canonical pathway, the expression is related with activation in the Nucleus Accumbens. Furthermore, we recently discover that stress during adolescence has an impact on cocaine-induced effect in adulthood. Intriguingly, we also found that the exposure to this early life stress influence the activity of the Wnt/β-catenin pathway, proposing that this signaling pathway could be mediating the proactive effect of stress on drug properties. In this manuscript, we cover different mechanisms that may underlie cocaine- and stress-induced changes in the Wnt canonical pathway. We also revise the idea of this pathway as a common target for adolescent stress and for the vulnerability to drug abuse later in life. We suggest that the canonical Wnt pathway constitutes a promising target that may open a door to new therapeutic strategies for the treatment of cocaine addiction.

Keywords: Wnt canonical pathway; Sensitization; Prefrontal cortex; Nucleus accumbens

Abbreviations

NAcc: Nucleus Accumbens; VTA: Ventral Tegmental Area; PFC: Prefrontal Cortex; CPu: Caudate Putamen; R: Receptors; D1 and D2R: Dopamine receptors; AMPA R: alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate Receptor; Ror: receptor tyrosine kinase-like orphan receptor 1; Ryk: Receptor like tyrosine kinase; Dvl: Dishevelled; GSK3β: Glycogen synthase kinase 3β; Wnt: Wingless-related integration site; LiCl: Lithium chloride; Amyg: Amygdala; i.p: intraperitoneal.

Introduction

In the last decades, drug addiction has been defined as a chronic and enduring phenomenon that has been extensively studied. The use of animal models has contributed to elucidate neurobiological bases of the different stages in the addiction process such as initiation, long-term use, and abstinence as well as relapse behavior. Animal models, such as behavioral sensitization, conditioned place preference and intravenous self-administration, have been extensively used. While the primary difference in these models is the way in which the drug is administered, the importance of the impact of non-contingent versus contingent drug administration in the molecular basis of addiction is under continuous debate. However, several similarities between behavioral sensitization and self- administration have been shown in terms of neurocircuitry and in terms of the molecular changes underlying the different behavioral responses [1].

In laboratory animals, the repeated administration of a psychostimulant (e.g. daily injections during a week) induced a progressive and enduring enhancement of the motor stimulant effects known as behavioral sensitization [2]. The development of this behavioral sensitization can be divided into two different domains termed induction and expression. The induction domain (a.k.a. or also known as initiation) refers to the immediate neural events caused by the psychostimulant and that induces behavioral responses; and, the expression domain refers to the long-term consequences of those initial events [1]. Usually the initial or short-term events are measured up to three days after the end of the repeated treatment with the psychostimulant; whereas the long-term ones are tested after a week and up to a year from the end of the treatment, mostly following a new psychostimulant challenge. While it has been extensively shown that changes in synaptic plasticity are involved in both the induction and expression of behavioral sensitization [1,3,4] each of these domains is characterized by specific molecular and neurochemical changes as well as by a given anatomical and temporal context. For instance, induction is linked to changes in the ventral tegmental area (VTA) and in the prefrontal cortex (PFC) [5–8] while expression is associated with changes in the nucleus accumbens (NAcc) [9,10]. Indeed, Ibotenic acid lesions in both prelimbic and infralimbic regions of the PFC disrupted the induction of sensitization [8]. Furthermore, different studies also suggested that a functional decrease of D2R in the PFC, induced by cocaine, would serve to enhance excitatory transmission to subcortical regions, a process known to be involved in the development of behavioral sensitization [11–14]. Regarding the long-term changes, cocaine induces a decrease in basal glutamate levels in the NAcc which increase after a cocaine challenge [7,15]. These higher levels of glutamate will act on the AMPA receptors (AMPAR) promoting higher behavioral responses [7,16]. Intriguingly, a cocaine challenge given after a period of withdrawal from cocaine exposure can transiently reverse long-term changes in the NAcc neurons. For instance, cocaine withdrawal induced an increase in synaptic strength of AMPAR relative to NMDAR-mediated currents because of an increase in the surface expression of AMPAR, which is temporarily reversed by a cocaine challenge [17–19]. Among other long-term neuroadaptations there are changes in dendritic spine density [20–23] that involve the regulation of the actin cytoskeleton [24,25], modifications in

the activity of small GTPase as well as the expression of different genes and their targets (e.g. ΔFosB, NFkB, Cdk5-MEF2, etc) [23]. Altogether, these evidences indicate that cocaine-induced sensitization is the result of an interaction between dopaminergic and glutamatergic neurotransmission (Figure 1A). Similarly, it has been demonstrated that, in laboratory animals, stressful situations during adulthood potentiate the effects of cocaine and other psychostimulants [26,27].

Role of the Canonical Pathway in Cocaine-Induced Long-Term Neuroadaptations

General Aspects of the Wnt Canonical Pathway

For the past years, in our laboratory we have been using the behavioral sensitization paradigm to model addiction-like behavioral responses to investigate the role of the Wnt (Wingless-related integration site) factors pathways. Wnt factors signals are

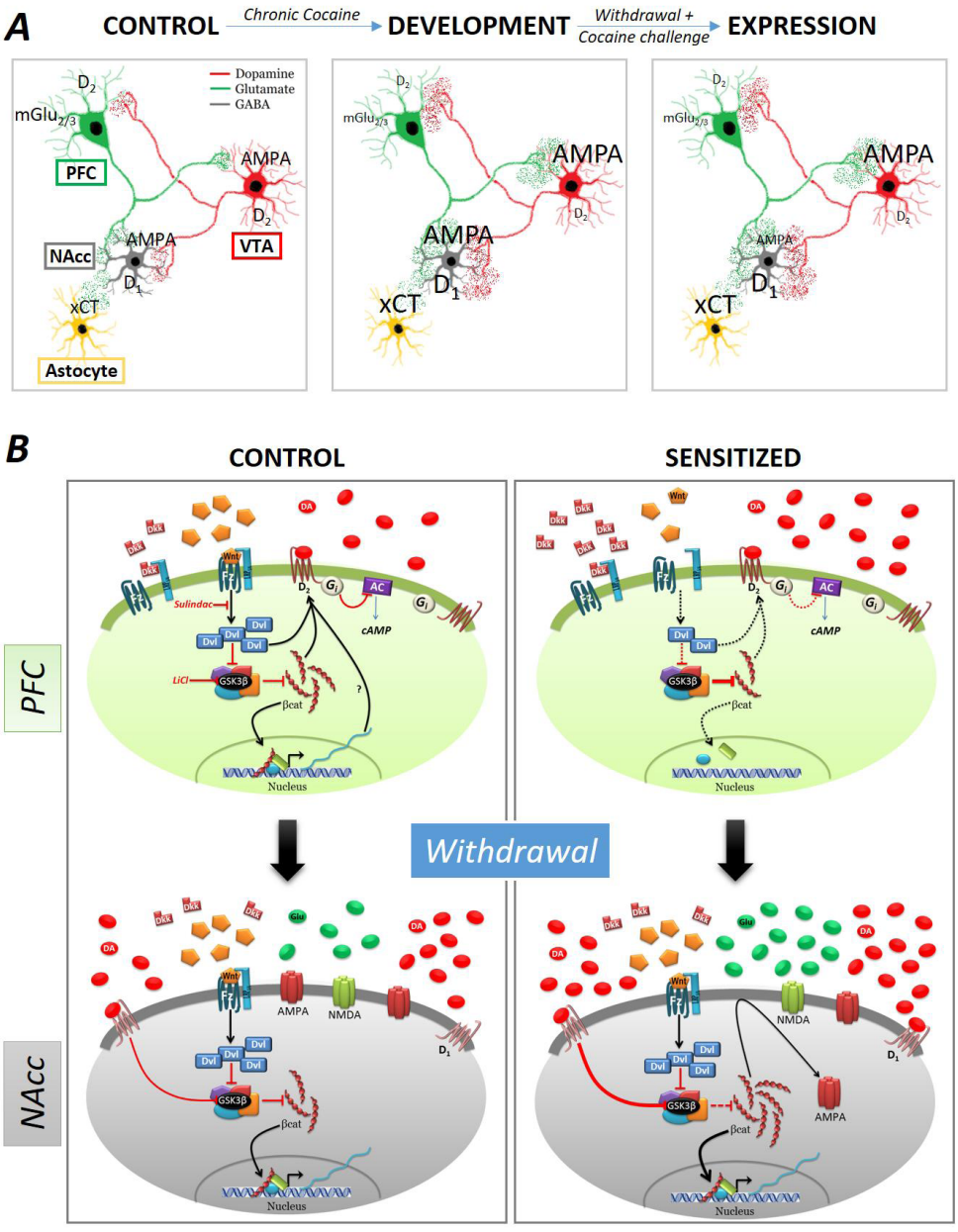

Figure 1: A) Summary of cocaine-induced neuroadaptations in the different receptors of the mesocorticolimbic circuitry that underlies behavioral sensitization. (xCT: Cystine/Glutamate exchanger; $mGlu_{2/3}$: metabotropic glutamate receptors; D_2: Dopamine D2-like receptor; D_1: Dopamine D1-like receptor; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor). B) Schematic representation of the neuroadaptations on Wnt canonical pathway in the PFC and in the NAcc of control and sensitized rats before and after withdrawal of chronic cocaine administration. Under control conditions, in the absence of Wnt, GSK3β phosphorylates β-catenin marking it for degradation by the proteasome. Upon activation of the Wnt canonical pathway, GSK3β is inhibited and leads to the stabilization of β-catenin and its subsequent translocation to the nucleus where it regulates the expression of Wnt target genes such as Axin2. (Dkk: Dickkopf-1; Dvl: Dishevelled; Fz: Frizzled receptor; D_2: Dopamine D2-like receptor; D_1: Dopamine D1-like receptor; Gi: Inhibitory G protein; AC: Adenylyl Cyclase; βcat: β-catenin; GSK3β: Glycogen synthase kinase 3β; DA: Dopamine; Glu: Glutamate; NMDA: N-methyl-D-aspartate receptor; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor). Black arrows: activation (filled: normal activity, dotted: reduced activity); red blunted arrows: inhibition (filled: normal activity, thickened: increased activity, dotted: reduced activity).

critical during the development of both the central and peripheral nervous systems. These factors are involved in a series of different processes including axon pathfinding, dendritic development, and synapse assembly. Wnt proteins also modulate basal synaptic transmission as well as the structural and functional plasticity of synapses in the central nervous system [28]. The Wnt growth factors are secreted proteins that can signal through different receptors such as Frizzled (Fz) [29], Ror2 and Ryk [30,31]. The interaction between Wnt and Fz leads to the phosphorylation of Dishevelled (Dvl), the first intracellular effector of the pathway. Once Dvl is phosphorylated, the Wnt pathways branch off in: the canonical or Wnt/β-catenin, the planar cell polarity and the Wnt/calcium pathways [32]. The activation of the Wnt/β-catenin pathway results in the phosphorylation of GSK3β Glycogen synthase kinase 3β leading to β-catenin stabilization. Once stabilized, β-catenin enters the nucleus, promoting the expression of different target genes of the pathway [29,33]. In the absence of Wnt, GSK3β phosphorylates β-catenin marking it for degradation by the proteasome [34]. At the extracellular level, a physiological antagonist, called Dickkopf-1 (Dkk-1), has been characterized for the Wnt canonical pathway. Dkk-1 is a secreted protein that, by binding the LRP6 co-receptor, specifically blocks the activation of the canonical Wnt pathway [35].

Wnt Canonical Pathway and Neuropsychiatric Disorders

Over the years, a great deal of evidence has shown an association between Wnt signaling dysfunctions and neurological disorders such as Alzheimer's disease, bipolar disorder and schizophrenia [36,37]. For instance, it has been shown that amphetamine (D2R indirect agonist) increases GSK3β activity and decreases β-catenin levels in the PFC and in the striatum, while the opposite effects were found with D_2R antagonists [38]. Notwithstanding the relevance of dopamine and its receptors to the effects of cocaine, little was known about the role of Wnt signaling pathways in drug addiction. Furthermore, it has been proposed that the regulation of GSK3β activity might be associated with cocaine-induced neuroadaptations. Chronic cocaine treatment induced changes in GSK3β activity in the striatum, while SB216763 and lithium chloride (LiCl), selective and non-selective GSK3β inhibitors respectively, prevent cocaine-induced sensitization [39–41]. Nevertheless, a direct link between the activity of the Wnt/β-catenin pathway and the changes found in GSK3β had not been proposed. Therefore, our main goal was to evaluate whether the Wnt/β-catenin pathway was involved in cocaine-induced neuroadaptations related with both the induction and the expression of behavioral sensitization. We combined molecular and behavioral studies with pharmacological strategies to evaluate the relevance of the Wnt canonical pathway for cocaine-induced behavioral sensitization [42,43].

Wnt Canonical Pathway and the Initiation of Cocaine-Induced Behavioral Sensitization

Experimentally, we worked with a well-characterized sensitization scheme developed by the Kalivas' Laboratory in the 90's [7]. This schema consists of an induction phase, involving seven injections of cocaine (2 × 15 mg/kg and 5 × 30 mg/kg, ip.) administered one per day followed by an expression phase evaluated after a cocaine injection (15 mg/kg, ip.) administered after three weeks of abstinence, on day 28. After the injections on days 1,7 and 28 of the treatment the locomotor activity was recorded for two hours. The remaining injections (30 mg/kg i.p.), between days two to six, were administered in the home cage. We considered that an animal was sensitized when it showed at least a 20% increase in the cocaine-induced locomotor response when comparing the first and last day of treatment (7 for development, 28 for expression) [7]. Different groups of researchers have demonstrated that not all the animals show an increase in their locomotor activity after the sensitization protocol is applied; only sixty percent does [7,8,18]. Likewise, we found that about 60% of the chronically-treated animals did show the increase in locomotor activity. Based on this criterion we divided the chronic-cocaine-treated animals into sensitized and non-sensitized according to their locomotor response. Then we investigated whether molecular changes in β-catenin, the final effector of the canonical Wnt pathway, were linked to cocaine-induced induction and expression of behavioral sensitization. In fact, we used β-catenin levels as a readout for the canonical Wnt signaling [33] in brain areas relevant to addiction such as the PFC, the NAcc, the Caudate Putamen (CPu) and the Amygdala (Amyg) in animals sacrificed 24 hs after the last injection on day 7 or 28.

Regarding the induction of sensitization, our main findings revealed that the animals that received chronic cocaine and developed the behavioral sensitization showed lower β-catenin levels in the PFC, CPu and Amyg when compared to saline-treated animals, while no changes were found in the NAcc. In line with β-catenin observations, we found that GSK3β activity levels were increased in the PFC, CPu and Amyg of sensitized animals. Furthermore, we found that in the PFC the nuclear levels of β-catenin the mRNA expression of Axin2 (a target gen of the pathway) and the expression of the mRNA of Wnt7b were decreased in sensitized animals. Taken together, these results reveal an inhibition of the Wnt/β-catenin pathway as an important neuroadaptation for the induction of behavioral sensitization, proposing a new role for this pathway.

In order to evaluate the importance of the changes in the activity of the Wnt pathway in the PFC for the development of sensitization we used two pharmacological approaches. The first one involved a systemic treatment with a well-characterized pathway activator as is LiCl [44]; while the second one consisted of intracerebral infusions of a pathway inhibitor called Sulindac [45]. Each treatment was administered before each cocaine injection. As expected, we found that LiCl, by preventing β-catenin reduction in the PFC as well as in the CPu and the Amyg, blocked cocaine-induced sensitization. In contrast, by facilitating the inhibition of the pathway in the PFC with Sulindac, the behavioral sensitization was exacerbated. Importantly, there was no impact on the behavioral response when infusing Sulindac in the CPu. These findings highlight the relevance of the inhibition of the Wnt canonical pathway in the PFC for the initiation of cocaine-induced sensitization.

Wnt Canonical Pathway and the Expression of Cocaine-Induced Behavioral Sensitization

When we focused on the expression of behavioral sensitization, we found that chronic cocaine induced an increase on β-catenin levels in the NAcc (both in total homogenates and in the nuclear fraction), a decrease in the CPu, and no changes in the PFC, when compared to saline treated animals. Once again, all these changes were only present in sensitized animals and entailed a cocaine-induced increase in the activity of the Wnt/β-catenin pathway in the NAcc.

On the Link Between Cocaine-Induced Behavioral Sensitization and the Wnt Canonical Pathway: Proposed Mechanisms Based on Previous Evidence

Taken together, our results proposed for the first time that changes in the Wnt/β-catenin pathway effectors are involved in the short and long-term neuroadaptations required for cocaine-induced behavioral sensitization. As previously mentioned, dopamine neurotransmission has been linked to intracellular effectors of the Wnt/β-catenin pathway [38,46–48]. Considering that cocaine-induced neuroadaptations include changes in dopamine and glutamate neurotransmission [1,23,49,50], it is possible that cocaine-induced changes in Wnt/β-catenin pathway

activity are linked to them. For instance, the cocaine-induced functional decrease of D2R in the PFC [11–14] could be related to the inhibition in the Wnt/β-catenin pathway. In fact Galli et al. [51] have recently demonstrated that inducible expression of the physiological inhibitor of the Wnt/β-catenin pathway Dkk-1 [35], in adult mice striatum decreases D1R and D2R clusters, leading to deficits in dopaminergic transmission. Hence, it is possible that the inhibition of the pathway induced by chronic cocaine is mediating the functional decrease of D2R observed in the PFC of the sensitized animals. Regarding the origin of this inhibition, a decrease in Wnt synthesis or an increase in Dkk-1 levels could be involved. However, the fact that we found significantly lower levels of Wnt7b mRNA in the PFC, after cocaine treatment, points out to a decrease in Wnt synthesis. Interestingly, Wnt7-Dvl signaling has been associated to presynaptic assembly and neurotransmitter release [52]. Furthermore, we showed that Sulindac, an inhibitor of the Wnt canonical pathway administered directly in the PFC facilitates the initiation of cocaine-induced sensitization. Because Sulindac acts at the level of Dvl, we hypothesized that the inhibition in the Wnt/β-catenin pathway observed in the PFC of sensitized animals may be associated with a functional decrease of Dvl leading to a disconnection of D2R. Regarding the levels of β-catenin in the PFC after a cocaine challenge on day 28, we found no changes when compared to controls regardless of the behavioral measurement. Interestingly, when we measured β-catenin in the PFC after a period of abstinence in sensitized animals, we found an increase when compared to the control group. In other words, our results propose that after a period of abstinence, β-catenin levels increase, but this increase is lowered back to control levels after a cocaine challenge, regardless of the behavioral outcome (sensitized or non-sensitized) induced by the drug challenge. It is possible that D_2R are involved in this mechanism as well as during initiation, but more experiments will be needed to clarify the relevance of these changes in cocaine-induced enduring neuroadaptations**.**

As regards to the long-term changes induced by cocaine in the Wnt/β-catenin pathway in the NAcc, two main modifications in the neurotransmission could be related with them: on the one side, the dopaminergic changes on receptor sensitivity and dopamine release in the NAcc [53–56], and on the other, the glutamatergic changes happening in this same area. In the case of the dopaminergic transmission, it is likely that the increased activation of the D_1R in the NAcc induced by cocaine causes the accumulation of β-catenin through inhibition of GSK3β [57]. This change could, in turn, further influence the glutamate transmission. It has previously been reported that three weeks of withdrawal from repeated cocaine increased the expression of AMPAR in the cell membrane of the NAcc and that this increase is reversed after a cocaine challenge only in behaviorally sensitized animals [8,18,58]. On the other hand, it has been shown that in hippocampal cell culture, the over-expression of β-catenin induces a rise in the total dendritic length and decrease the density of surface synaptic AMPAR clusters; mimicking the effects of an increase neuronal activity [48]. Therefore, it is possible that the cocaine-induced increase in β-catenin levels mediated by dopamine in the NAcc activates the pathway as well as facilitates the removal of AMPAR from the surface after the cocaine challenge, giving rise to the expression of behavioral sensitization. On a side note, we emphasized on the long-term effect in this area because our results did not show any immediate influence on the pathway in NAcc. However, it is possible that the fact that we did not sample the NAcc in core and shell could hide small changes.

Interestingly in the CPu, we found that both development and expression of sensitization are associated with lower levels of β-catenin only in animals that showed behavioral sensitization after a challenge, while it was significantly increased after three weeks of abstinence, similar to what happened in the PFC. Taken together, these results suggest that behavioral sensitization requires a reduction in β-catenin, below basal levels, in order to manifest. However, in the case of development of sensitization in the CPu, we also found that nuclear levels of β-catenin were similar to the control ones, and forcing the decrease (by infusing an inhibitor) was not enough to induce the behavioral sensitization. In other words, it seems that this decrease is necessary but not sufficient for the development of sensitization. In the case of the expression of sensitization, changes in β-catenin, and probably in the activity of the Wnt canonical pathway, might be more important and could be mediated by the dopaminergic transmission through D2R. It has been shown that repeated drug exposure leads to a reduction in striatal D2R levels [59]. Therefore, and considering that the antagonism of D2R is linked to β-catenin accumulation [46], while the activation is associated with β-catenin degradation [60], it is possible that chronic cocaine facilitates the accumulation of β-catenin found in the CPu of abstinent animals. Although the fact that β-catenin levels in the CPu increase during withdrawal and decrease after a challenge only in the sensitized animals suggests that activity of the Wnt/β-catenin pathway may be a characteristic of long-term neuroadaptations, further experiments must be done to clarify the relevance of these findings.

In our studies, we also demonstrated that the activation of the canonical Wnt pathway induced by LiCl administration before each cocaine injection not only prevented the development of sensitization by restoring β-catenin levels in the PFC, CPu and Amyg, but also prevented the expression of behavioral sensitization by keeping the levels of β-catenin increased in the NAcc. Previously, we proposed that the increase in β-catenin levels in the NAcc, together with its decrease in the CPu, are correlated to the behavioral changes. Initially these results obtained by using LiCl seemed contradictory. However, if we consider that it is β-catenin fold-change that dictates Wnt pathway activity and not just the absolute level [61], then the LiCl results strengthen the idea that it is the change in β-catenin and the consequent activation of the canonical pathway that matters for the expression of sensitization. To our knowledge, this is the first time data reported that LiCl has enduring effects on cocaine-induced neuroadaptations. To understand the mechanism underlying the long-term effect of LiCl on cocaine-induced behavioral neuroplasticity it might be necessary to look into further effects along the motivational circuitry. As mentioned before, we have shown that by preventing the inhibition of the canonical Wnt pathway (i.e. keeping β-catenin levels similar to control) in the PFC and CPu it is possible to block the initiation of behavioral sensitization [43]. These restorations could interfere with the subsequent enduring effects of cocaine. Moreover, we showed that when LiCl is administered with cocaine, it induces an increase in the β-catenin levels of the NAcc, visible up to 3 weeks after the end of the treatment [42]. It is possible that this enduring increase in β-catenin levels may have an impact on the surface expression of AMPAR in the NAcc, reducing them [48], as well as in the cocaine-induced behavioral response during the expression of sensitization. Furthermore, it has been recently showed that LiCl decreased DA release in the NAcc [62] which can also affect the cocaine response.

Altogether, our results indicate a new role for the Wnt/β-catenin pathway in cocaine-induced neuroadaptations strengthening the importance of the PFC-NAcc connections as biological substrates of cocaine-induced behavioral sensitization (Figure 1B). By using different strategies, we demonstrated the relevance of the inhibition of the Wnt/β-catenin pathway in the PFC both for short and long-term neuroadaptations induced by cocaine. Specifically, we showed that if we activate the pathway by administering LiCl,

then cocaine is not able to induce development or expression of sensitization. Furthermore, only the inhibition of the pathway in the PFC (by Sulindac infusion) exacerbates the development of sensitization, while no effect was found with Sulindac infusions in the CPu. Keeping all these results in mind, we postulate that the initial inhibition of the canonical Wnt pathway induced by chronic cocaine in the PFC results in dramatic changes in the expression of different target proteins of the pathway, altering the communication between the PFC and the NAcc. This modification in the circuitry would be related, after a withdrawal period, with the changes in the pathway´s activity in the NAcc and also with the behavioral response induced by a cocaine challenge.

Long-Term Impact of Adolescent Social Isolation on Cocaine-Induced Motor Activity: Possible Role of the Wnt Canonical Pathway

It has been shown that previous exposure to stressful situations during adulthood induced sensitization to the psychostimulant effects of amphetamine and cocaine, an effect mediated by an interaction between dopaminergic and glutamatergic neurotransmission in the NAcc [26,50,63,64]. However, the long-term consequences of adolescence stress exposure are less known.

Recently our lab showed that five days of social isolation during adolescence (PND 30–35) increase the impact of cocaine-induced sensitization during adulthood when compared to non-isolated animals [65,66]. Specifically, we found that in the group isolated during adolescence the exposure to a cocaine treatment -characterized by a lower total dose of cocaine compared with the one used before in [42,43]- induced a higher rate of behavioral sensitization during adulthood. Moreover, we found that this increase in the rate of sensitization is related to an upregulation in the activity of the Wnt/β-catenin pathway in the NAcc measured the day after the last cocaine injection, but with no changes in the PFC. Interestingly, we also found that adolescent social isolation by itself alters the expression of Wnt canonical pathway effectors in the PFC. Specifically, β-catenin level is decreased while GSK3β activity is increased in the PFC for at least 10 days after the isolation, suggesting that social isolation induces a long-lasting decrease in Wnt canonical pathway activity [66].

Adolescent Social Isolation and Cocaine Share a Long-Term Impact on Wnt Canonical Pathway

The stress-induced changes on the canonical pathway mentioned above resemble the ones induced by a cocaine treatment the day after the last cocaine injection in sensitized animals [43]. Furthermore, in the case of cocaine-induced sensitization, we suggested that decreased activity in the PFC has a long-term impact on the motivational circuit that allows the expression of cocaine sensitization (Figure 2A). In line with these hypotheses, we proposed that the exacerbation of cocaine sensitization in previously isolated adults compared to non-stressed animals might be linked to the

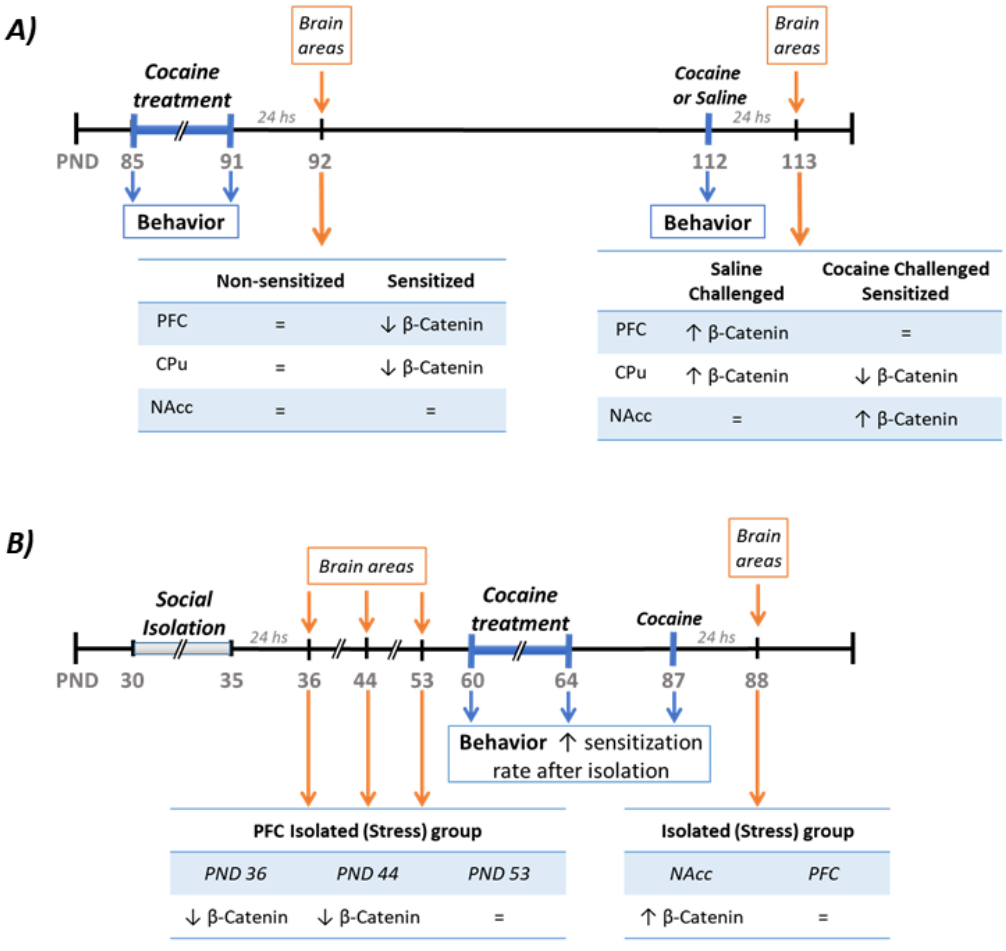

Figure 2: Schematic summary of the experimental procedures as well as the results. A) Summary of cocaine-induced sensitization and the changes in β-catenin levels found at the different time points. B) Summary of isolation experimental procedure as well as the cocaine sensitization paradigm use after isolation. The changes in levels β-catenin levels found at the different time points are also described.

reduction in the Wnt/β-catenin pathway activity in the PFC found 24hs after five days of isolation (Figure 2B). While this is the first demonstration that previous stress exposure has a long-lasting effect on the activity of the pathway, which may exacerbate the impact of cocaine later in life, it is not the first evidence that shows the Wnt pathway in the NAcc is associated to stress responses [67]. Therefore, we postulate that the Wnt/β-catenin pathway is another molecular mechanism that can be incorporated into the mounting evidence that supports the interchangeability between stress and drug effects. Importantly, we suggest that the canonical Wnt pathway should be considered as a mechanism involved in the individual vulnerability to drug effects.

Conclusions

Since locomotor sensitization in rodents seems to share plastic mechanisms with drug addiction in humans, and corresponds to aspects of drug abuse such as initiation and compulsive drug-seeking behavior (for review see [1]), our findings suggest that the Wnt canonical pathway may be involved in the early stages as well as in relapse of substance abuse. Furthermore, we find that this pathway may represent a common target for the long-term effects of adolescent stress and the increase in the vulnerability to drug abuse later in life. Although one must always be wary of extrapolating clinical relevance from animal data, the considerations discussed above suggest that the Wnt pathway constitutes a promising target for the development of a treatment for addiction. Consequently, our findings may open a door to new therapeutic strategies for the treatment of cocaine addiction.

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Conflict of Interest

The authors declared there is no conflict of interest.

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